International

RECORD OF MEDICINE

A Journal of Advanced Experimental and Clinical Reports

and

GENERAL PRACTICE CLINICS

ORIGINALLY PUBLISHED AS AMERICAN MEDICAL INTELLIGENCER, FOUNDED PHILADELPHIA, 1837

WHOLE NUMBER 2825

VOL. 164 NO. 11

NOVEMBER 1951

ORIGINAL ARTICLES

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II. Ultrasonometry: A New Modality in Biology and Medicine

III. Dichotomous Quantitative Differentiation (DQD) of Hematosonographs of Psychotics from Nonpsychotics

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Oral Nonspecific Therapy — *Howard B. Emerson*

ABSTRACTS

Conference on World Population Problems and Birth Control

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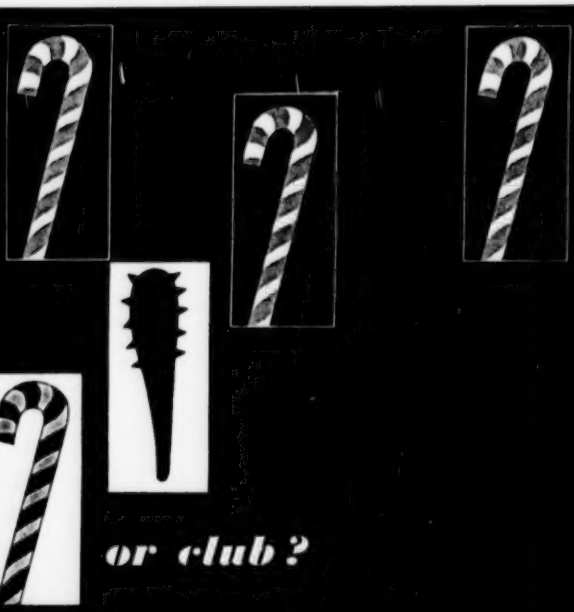

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VOL. 164 NO. 11 • WHOLE NUMBER 2825 • NOVEMBER 1951

Published Monthly by

THE WASHINGTON INSTITUTE OF MEDICINE

3801 CONNECTICUT AVE., N. W., WASHINGTON 8, D. C.

Félix Martí Ibáñez, M.D.

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19½ East 62nd Street, New York 21, N. Y.

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667 Madison Avenue, New York 21, N. Y.

A cumulative cross reference index is included in the final issue of each volume. Subscription rate: 1 year, $7.50; 3 years, $15.00. Copyright 1951 by Washington Institute of Medicine. Entered as second class matter at Washington, D. C. under the Act of March 3, 1879. Printed in U. S. A.

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INTERNATIONAL RECORD OF MEDICINE

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GENERAL PRACTICE CLINICS

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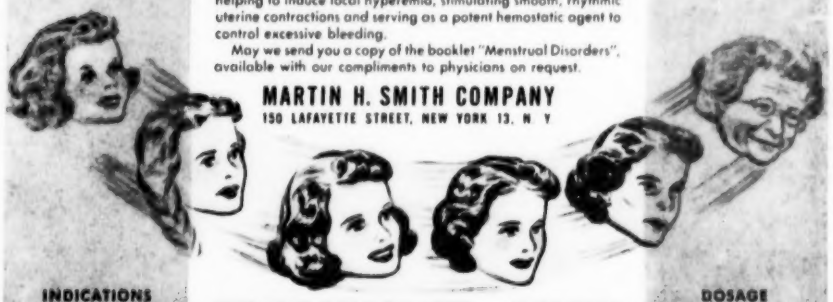

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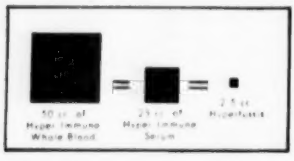

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Editorial

Since 1837 when it was founded and since the days when Osler and others published some of their best scientific papers in this Journal, the Record has taken the utmost pride in publishing original articles, many of which are today a part of our most distinguished medical heritage.

In this issue, we are presenting the paper "Quantitated Identification of Psychoses by Blood Sample." This report may well mark the historic point in the advance of psychiatry at which this branch of the medical sciences changed from qualitative impressions to quantitative measurements. It may thus be a landmark in the history not only of psychiatry, but also of biology and medicine. Such changes in methodology are fundamental if we are to convert finally all clinical medicine from empirical art to pure science.

With this research a new field of the medical sciences—termed by the authors "hematosonography"—has been introduced, a differentiating test for psychoses demonstrated, and the participation of biochemical factors in the pathogenesis of mental disorders has been made more accessible to study.

For those who have been associated with or have closely followed the work of the Drs. Sacklers and their associates at Creedmoor and the van Ophuijsen Center, the differentiation of psychotics from nonpsychotics, purely by the application of physics and mathematical measures to a specimen of blood, is the logical outcome of a long chain of experiments incorporating the philosophy and techniques of physiology and biochemistry into psychiatric investigation. It is a fitting sequel to their paper, "Physiodynamics of Some Major Metabolic Disorders," wherein they formulated a general theory which enabled them to predict in 1949 that cortisone, ACTH, and adrenal cortical hormones would produce or precipitate psychoses in some individuals even as it could benefit other psychiatric states. It is consonant with the authors' basic thesis of the last five years that endocrine dysequilibria, in particular an operative excess of protein catabolic adrenocortical hormones, underlie such psychiatric processes as the schizophrenias and that such an excess must be reflected in changed characteristics of the blood. The new technique whereby this has been demonstrated is hematosonography. It employs an apparatus in which electronically generated ultrasonic waves are used in the quantitative analysis of the changing viscosity and/or other physical properties of drawn blood undergoing the clotting process. The machine it-

self, an ultrasound viscosimeter, had been developed for use in the measurement of viscosity of fluids used in industrial processes. The autographically recorded HSG curve is then analyzed mathematically. The results are pure objective determinations. The mathematical quantitation of an aspect of our "art and science," which has been more closely related to philosophy than to physics, may come as a shock to some.

Further, the demonstration that psychotics who are receiving such hormones or substances as the sex steroids, thyroid, and histamine could be differentiated from those not receiving them, again on the basis of a blood sample and mathematical formulations, suggests major opportunities not only for psychiatry, endocrinology, and hematology but for every branch of medicine as well. The authors have recognized that implicit in their findings are evidences which point to possible applications in cancer and generally in metabolic, physiologic, pharmacologic, and hematologic research. The findings also suggest practical procedures, for the "mass screening" of large groups for military and civilian purposes may well prove a medical landmark rivaling the ECG and EEG and surpassing their scope of applicability.

The historic roots of this method spring from the philosophy created by Descartes in 1637 with his "Discourse du Methode" and from the philosophy of such scholars as Giorgio Baglivi, Professor of Anatomy in Rome (1668-1706), who said, "*The two chief pillars of Physics are reason and observation*" (Depraxis medica); the Hunter Brothers in England, who made of scientific experiment a basic tool of medical science instead of purely theoretical speculation; and the Spaniard, Ramon y Cajal, whose lucid and practical work in nervous histology won him the Nobel prize in 1906. Thus, today the most qualitative of medical disciplines—psychiatry—may pioneer as a quantitative science of measurable magnitudes.

Medicine has recently developed a trend in which attention to the technical details and isolated ideas tends to overshadow the broad concepts of which the isolated fact is but a part, so that the forest of the broad concept of general principle is lost in preoccupation with the details of the tree of an isolated idea. Such a continuing trend could well lead medicine into mere technology. For this reason, we must be grateful to these authors for contributing to a countertrend to restore a balance between the philosophy of the general scientific theory and the technology embodied in the isolated fact. It is also significant that their views as to the participation of hormonal factors in mental disorders and some of their dynamic physiologic concepts are finding adherence and substantiation in contemporary literature. Such broad-gauged concepts deserve extensive study and test in the hands of a wide circle of investigators.

Psychiatry has traditionally been a qualitative science. Through the centuries, this Cinderella of medicine and its nosology have been based on the medical pathology of the prevailing times. Iatrophysicists tried to find a medical explanation for psychiatric disorders in the velocity of the blood, following the ideas of Borelli and Sanctorius of the preceding century. The most daring step ever taken to give psychiatric research an objective basis was that of Lorenzo Bellini and Richard Morton, iatrophysicists of the XVIII Century, who, in an attempt to explain the "delirium of fever," said that fever (*delirium*) was induced by the "increase in the velocity of the blood, which caused interference with the secretion of the glands of the brain." By the end of the XIX Century, psychologic tests were being developed and were later used in

the diagnosis and prognosis of mental diseases, but the approach continued to be subjective. Variations in the emotional condition of the patient, and sometimes subjective variations in the psychiatrist himself, influenced the interpretation and even the results of most psychologic tests used in psychiatry. Hematosonography, as applied to psychiatry by the authors, is not a resurrection of iatrophysic or iatrochemic philosophies. It does not seek to make of the human organism a test tube as iatrochemics, or a machine as iatrophysics. The new method, based on observation and experimentation, is used to further the integration of interrelated physiologic findings. It marks an *epoch in the use of quantitative data in medicine and signifies closer collaboration between clinical observers and experimental investigators.* By introducing physics and mathematics—the two royal sciences of our century—into psychiatry a long-hoped-for extension of medical horizons may be ushered in.

The use of hematosonography in psychiatry and medicine represents another great step forward in the historical progress of the instruments used in quantitative analysis since Sanctorius introduced a tool to "count" the pulse in the XVI Century. This progress, which includes a "pulse-watch" developed by Sir John Floyer in the XVIII Century; an apparatus to measure blood pressure produced by Reverend Stephen Hales in 1733; the haemocytometer, introduced by Gowers in 1878, and followed later by the electrocardiograph, electroencephalograph, and other machines in conjunction with which came the use of the numerical method introduced by Pierre Charles Alexander Louis, and the statistical method suggested by the physicist and mathematician, Jerome Cardan, and developed by Galton, on the premise that it was not enough to register mensurations, but that it was also necessary to analyze them objectively.

All these instruments—from the clinical thermometer of Sanctorius to the hematosonograph—mark the progress from qualitative impressions to quantitative measurements. They were not intended to replace sound clinical judgment. They do supply concrete data and exact factors with which to elaborate a final judgment.

For the first time in the history of medicine, through the concerted efforts of several scientists, physicists, and biostatisticians, a technique has been developed which, in our opinion, not only will introduce a new and revolutionary diagnostic and prognostic approach in psychiatry, but will also lead to the solution of many of those riddles of the physiology of the blood which have persistently remained unsolved. The application of ultrasonometry to other fields of medicine and the use of the new physical techniques and their mathematical analyses will make it possible to study a vast number of phenomena of great diagnostic, prognostic, and therapeutic value. They may facilitate the study of the hormones of the blood and their relationship to good health and disease; they may make possible the control of dosage and effect of drugs whose administration is still empiric in medicine. They may establish the basis of a new philosophy in scientific research that will use only the most advanced physical and mathematical tools of the XX Century and that will offer the scientific mind quantitative data upon which to base its criteria.

In publishing these important papers, we welcome a truly revolutionary technique in psychiatry, a new science to be incorporated in the history of medicine. A "*nova scienza*" has been born and we are proud to be the first to salute it.

Instrumentation Of Ultrasound For Biologic Quantitation*

PART I OF QUANTITATED IDENTIFICATION OF PSYCHOSIS BY BLOOD SAMPLE

Raymond R. Sackler, Stanley Rich, Wilfred Roth, Mortimer D. Sackler, Co Tui, Félix Martí Ibáñez and Arthur M. Sackler

CREEDMOOR INSTITUTE FOR PSYCHOBIOLOGIC STUDIES
CREEDMOOR STATE HOSPITAL, THE VAN OPHUIJSEN CENTER

Signals reflecting the absorption of ultrasonic energy in a liquid are analyzed in an electronic computer, displayed continuously on a calibrated viscosity meter and recorded autographically.

Our conviction of the participation of neuroendocrine factors in the pathogenesis of the schizophrenic process grew out of clinical observation and a series of investigations previously reported. These elucidated biologic differences between hospitalized and non-hospitalized schizophrenics and between these psychotics and psychoneurotics. The possibility that these differences could eventually be used for differentiation of patients and analysis of the processes at work led us to seek suitable biochemical and physical tests. The present report presents a new development in our efforts to achieve biologic quantitation in psychiatric studies and indicates the practicability of ultrasound as an instrument for dichotomous quantitated differentiation (DQD) of psychotics from nonpsychotics.

Several of the authors (A. M. S., M. D. S., R. R. S., and C. T.) had reported previously a difference in clot behavior between psychotic and nonpsychotic individuals, indicating that finer measurement of this biophysical phenomenon might yield critical information. However, the crudity of quantitation of routine clotting tests and also of our syringe test led to the utilization of an ultrasonic device† invented by Stanley R. Rich and Wilfred Roth, physicists, to measure the changes in viscosity of liquids. This instrument was originally designed to utilize ultrasonics (elastic vibrations above audibility) for automatic and continuous measurement and autographic recording of viscosity**

*Reprinted from J. Clin. Exp. Psycho. *12*:283-287, Oct.-Dec. 1951.

†The Ultra-Viscoson is a product of the Rich-Roth Laboratories of East Hartford, Connecticut.

**Viscosity is that property of a liquid or a gas that resists flow or change of shape. If two parallel plates each 1 $cm.^2$ in area are separated by a layer of liquid 1 cm. thick, the viscosity of this liquid, *by definition*, will be 1 poise if 1 dyne of force is required to pull one plate parallel to itself at a velocity of 1 cm. per second with respect to the other plate. Thus, viscosity is a measure of the "internal friction" of a fluid. The molecules of a liquid are in continual motion as a result of their thermal energy, and this motion increases directly with the absolute temperature. In a given imaginary plane surface in a liquid, molecules will be continually crossing this surface in both

changes of liquids and semi-liquids in chemical reactions including polymerization, production of synthetic rubber, blending and fractionation of petroleum products, blood extenders, and the like.* In brief, the instrument comprises an ultrasonic probe and an electronic automatic computer. The probe is an all-metal, ultrasonic transducer which is hermetically sealed and is designed to operate continuously over the temperature range —150° F. to 650° F. and in pressures from vacuum to thousands of atmospheres. The design of the probe is such that samples of liquid can be measured from 4 c.c. or less to thousands of gallons in containers varying in size from test tubes to industrial processing vats. The sensing element of the probe is a thin blade of a springlike alloy steel which protrudes from a stainless steel barrel or container as shown in the photograph.

Ultrasonic waves are produced by the probe in the liquid in which it is immersed. If sufficient liquid surrounds the probe, minute layers or laminae are caused to slip back and forth over one another at an ultrasonic frequency, the laminae experiencing bidirectional or alternating motion.† The electronic computer attached to the probe by a cable of any desired length, instantly calculates the viscosity of the liquid from the effect of the interaction of the ultrasonic waves with the molecules of the liquid. The result is graphed automatically by an electronic recorder.

For accurate measurement of physical changes in blood, care must be used to standardize a definite volume and container since the physical characteristics being measured may be altered by the quantity of the blood and physical characteristics of the container.** Once the minimum critical volume essential‡ for measurement is exceeded, the instrument reading is given by:

directions as a result of this thermal agitation. The higher the temperature of the liquid, the more molecules cross the surface per unit of time.

If the liquid on one side of the imaginary boundary is caused to move with respect to the liquid on the other side, the molecules that cross the boundary from the moving liquid have a larger component of motion parallel to the surface than do those crossing from the stationary liquid. The interaction of these will tend to prevent motion of the moving liquid and to produce motion of the stationary liquid. This can be recognized as a phenomenon similar to sliding friction, although it is termed viscosity when reference is made to liquids. Since the rate of molecular exchange across the imagined plane surface increases with temperature, equilibrium would be reached more rapidly at higher temperatures. This has been experimentally supported in the finding that viscosity decreases as temperature increases.

*The instrument has been and is being used for the study of thrombo-embolic phenomena and hemorrhagic tendencies by Drs. Raymond Yesner and Alfred Hurwitz at the Newington Veterans Administration Hospital, Newington, Connecticut.

†With concentrated high-polymer solutions, the difference between this bidirectional as compared to unidirectional motion is important for reasons beyond the scope of this paper, but for our present blood investigations, it is of only minor importance.

**Glasser reports in Medical Physics, Vol. 1, p. 217, 1950, Yearbook Publishers, that blood serum and plasma are both Newtonian liquids, but whole blood is Newtonian only if the diameter of the capillary tube in the above experiment is greater than 0.4 mm. If smaller bores are employed, the viscosity characteristic of whole blood will resemble that of a thixotrope—viscosity will decrease as the pressure increases. In living capillaries, blood flow exhibits a yield point due to interaction of the blood with the capillary walls. In this type of flow, we have a pseudoplastic. The non-Newtonian nature of whole blood can be traced to the fact that it is a suspension; i.e., gross particles, e.g., red cells, white cells and platelets, are present in suspension.

‡Since the Ultra-Viscoson requires a minimum depth of 0.3 mm. of liquid on the probe and since the blade is only 5 cm. long, very small volumes can be handled.

$$\text{Meter Reading} = \frac{\rho}{\omega\omega} \left(\sqrt{g^2 + \beta^2 \eta^2} + g \right) \qquad (1)$$

Where: ρ = density of liquid (gms. cc.)
$\omega\omega$ = constant of the system
g = rigidity coefficient of liquid (dynes cm^{-2})
η = viscosity coefficient of liquid (poises)
β = frequency employed

For the majority of liquids, including blood, the rigidity is completely negligible and $\beta = \omega\omega$. Therefore, we obtain

$$\text{Meter reading} = \rho\,\eta \qquad (2)$$

as the response of the instrument.

The viscosity appears continuously on a meter calibrated in c.g.s. units of viscosity: —centipoises (poises x 10^{-2}) times density in grams per cc. Four ranges are provided: 0-50, 0-500, 0-5000, 0-50,000 centipoises x grams cc. In these blood studies, only the 0-50 cp. range is utilized. A permanent graph is drawn autographically by an attached recorder, in this instance the Brown Electronik Potentiometer. The recorder chart, driven at constant speed by its synchronous chart drive motor, (2 inches in 4 minutes) automatically indicates time, while a curve is traced autographically by the recorder pen (with a speed of 4½ seconds, full scale).

Routine calibration is readily made on a Newtonian oil* of known viscosity as a standard. A control in the computer is readily adjusted so that the indicating meter reads exactly the viscosity times the density of the standard. The instrument is then operating under calibrated conditions in terms of absolute, fundamental quantities.

*In general, liquids can be categorized as Newtonian and non-Newtonian. If a liquid is made to flow through a capillary tube by applying a pressure difference across opposite ends of the tube, curves of flow velocity versus pressure difference can be plotted. A Newtonian liquid will obey a strict linear relationship as shown by curve 1, Fig. 1. All materials not exhibiting this linear behavior are, *by definition*, non-Newtonian.

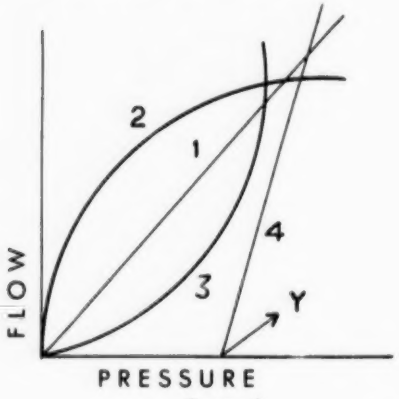

FIGURE 1

Curve 2 is that of a material having low viscosity at low pressures and high viscosity at high pressures. Starch solutions behave in this way. Such materials are called dilatants. Curve 3 is the opposite of a dilatant and represents a liquid called a thixotrope. Many colloids, suspensions, slurries, etc., are thixotropic, and, therefore, are difficult materials with which to work. Curve 4 is that of an ideal plastic. Here we must exceed a critical value of pressure, Y, termed the yield point, before any flow occurs. Once the yield point is exceeded, a true plastic behaves as a Newtonian material. There are many other possible types of non-Newtonian materials, but they exhibit characteristics similar to those already discussed.

FIG. 1. From left to right. (1) Ultraviscoson probe above and centrifuge tube in constant temperature water bath. (2) Ultraviscoson unit. (3) Potentiometer.

Ultrasonic waves are propagated by the probe which is immersed in blood in the centrifuge tube. The electronic computer with the ultraviscoson unit is attached to the probe by a cable and instantly calculates the changing viscosity of the blood as it clots. The result is graphed automatically by an electronic recorder (potentiometer above).

SUMMARY

Materials that change their physical characteristics with time, temperature, pressure, etc. are difficult to study unless viscosity can be measured instantaneously, continuously and automatically. Among biologic liquids, blood is most typically such a substance. Thus, quantitation of certain of its physical characteristics has long constituted a problem. The utilization of ultrasound made possible instantaneous, continuous and automatic study of viscosity and or other physical changes. In conjunction with standard recorders, these changes can be autographically recorded. These instruments are applicable for study of physical changes in blood and have here been utilized in an attempt to quantitate a specific physical characteristic differentiating blood of psychotic from that of nonpsychotic individuals.

ACKNOWLEDGMENTS

Any work such as this has a history—a history in terms of individuals. There are a number who, though not listed as authors, have contributed so significantly that these investigations would not have been possible without them.

Among them are three men whose convictions that the needs of mental patients can only be better served by research were so firm that they gave their support despite opposition. To these three men, Drs. Newton J. T. Bigelow, H. B. Lang, and Harry A. La Burt, our deepest appreciation for their staunch support and inspiring confidence.

For acuity of clinical observation, special reference should be made to Helen Klous, R.N., who first noted that syringes used in drawing blood from psychotics did not usually "freeze" when left untouched for a period of time.

For the unfailing and unflagging trouble-shooting and very real contributions of Heinz Norden, our sincere gratitude.

For sympathetic, intelligent, and unfailing attention to the patients of Creedmoor Institute, and full cooperation in this work, our thanks go to Eileen Jacoby, R.N., Ann Nicoll, R.N., Eleanor Alesi, R.N., Elaine Kremens, and Charlotte Grossman.

For enthusiastic participation, our thanks to psychologist Karl Steinman.

For the untiring and devoted efforts of Elizabeth Short, Florence Levin, Miriam Kent, Leemarie Burrows, our warm thanks.

On this occasion we also wish to extend our welcome and appreciation to the several new members of the Institute staff who have cooperated in this project: Dr. Rosaltha Sanders, Mrs. Lily Schmidt, and Dr. Constance Martin.

And last, but not least, our heartfelt thanks to those contributors to and "victims" of such research—the wives, children, husbands, and families of all those actively participating.

It is also fitting to note that the first of these series of investigations leading to this work were initiated at the van Ophuijsen Center with the participation of the late Johan H. W. van Ophuijsen, M.D., F.A.P.A., first Clinical Director of The Creedmoor Institute.

The cost of equipment, personnel, and other expenses were endowed by grants made in the memory of Isaac Sackler.

It is particularly fitting that the senior author of the first paper be Dr. Raymond Sackler, since it was at his insistence that ultrasound was added to our biologic investigative techniques.

Ultrasonometry: A New Modality In Biology And Medicine*

PART II OF QUANTIATED IDENTIFICATION OF PSYCHOSIS BY BLOOD SAMPLE

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CREEDMOOR STATE HOSPITAL, THE VAN OPHUIJSEN CENTER

A. CHARACTERISTICS OF THE HEMATOSONOGRAPH (HSG).

Research leading to hematosonography is reviewed. Nomenclature is proposed, and a composite hematosonograph (HSG) is presented. Certain specific quantitatable characteristics are elucidated.

B. COMPARISON OF HEMATOSONOGRAPHS (HSG) OF PSYCHOTICS AND NON-PSYCHOTICS

Analysis of certain quantitated factors of the hematosonograph (HSG) reveals variations characteristic respectively of psychotics and nonpsychotics. Following analysis, statistically significant factors are isolated for scoring.

C. HEMATOSONOGRAPHY OF OXALATED BLOOD AND PLASMA

Hematosonographic curves of oxalated blood differ from those of nonoxalated blood. These findings, as well as preliminary studies with plasma, are discussed.

There has been need for improved instrumentation to quantitate more precisely progressive changes in biologic fluids. In this study the varying damping effects on ultrasound of a fluid whose physical characteristics are changing is utilized for purposes of quantitation. The use of ultrasound for measurement of certain physical properties is termed ultrasonometry (USM). The application of ultrasonometry to the biologic fluid blood, together with the autographic recording of the measurement, is herewith designated hematosonography or hemosonography (HSG). The tracing or curve from which the measurements are taken is termed the hematosonograph or hemosonograph (HSG curve).

This section records the background of the investigations which led to hematosonography. It outlines our current hematosonographic procedures and presents nomenclature for identification of the nodal points of the curve and its characteristic segments, particularly those with quantitatable attributes referable to the present investigation.

BACKGROUND

In 1948, skin testing with histamine was investigated in psychotic and nonpsychotic individuals by three of the present workers (A. M. S., M. D. S. and R. R. S.) and the late Dr. van Ophuijsen. Although promising, difficulties were encountered in quantitating

*Reprinted from J. Clin. Exp. Psycho. *12*:288-303, Oct.-Dec. 1951.

the resultant observed skin flare and wheal. In 1949, four of the present workers, (A. M. S., M. D. S., R. R. S. and C. T.) and Dr. van Ophuijsen again attempted to differentiate psychotic from nonpsychotic by the utilization of a phytoassay procedure in which rose buds were placed in urine and observed over a period of days. This study was also complicated by problems of quantitation.

Beginning in 1950, attempts were made by the authors to quantitate the observation that syringes into which had been drawn blood from psychotics and which were then kept for twenty-four hours with the plunger fully inserted, did not "freeze" or "jam" as consistently or as frequently as those with blood drawn from nonpsychotic individuals.

The "syringe test" was applied to over 194 psychotics and over 78 controls. Although the results were suggestive of a difference, a number of variables were present which were difficult to control, e.g., the grinding of the syringes and the force used to remove the barrel. However, some preliminary work with the "syringe test" was reported earlier this year at the Downstate (N.Y.) Interhospital Conference[1] and at the First Anniversary Dinner of The Creedmoor Institute.[2] The original observation of a possible abnormality in the blood of psychotics found support in Dr. H. B. Lang's experience with naval personnel.[3] He had noted that oozing from venipuncture site some time after aspiration suggested empirically that the individual be carefully studied for "immaturity."

REVIEW OF HEMATOLOGIC AND RELATED STUDIES

Many hematologic parameters have been subjected to scrutiny at one time or another in an attempt to elucidate a difference in the blood of psychotics. Meduna et al,[4] Katzenelbogens,[5] Freeman et al,[6,7,8] Hoskins,[9] Kety et al,[10] and others[11-20] have studied not only the levels of blood constituents but also their response to varied physiologic stimuli. The evidence seemed to indicate that the only consistency was inconsistency or variability of the parameters in schizophrenic patients. In 1941, Gilea [21] stated that examination of the body fluids of psychotics and nonpsychotics revealed no significant difference. However, the use of physiologic stimuli, such as in the glucose tolerance test, has since indicated that at least a difference in response is often shown by the psychotic. Abnormal glucose tolerance in schizophrenics has been reported and has also been shown by other workers and ourselves to improve as the clinical status of the patient improves.

The blood eosinophile level and its response to ACTH and other physiologic stimuli have been studied in psychiatric disorders by Finn Rud,[22] Altschule, Parkhurst and Tillotson,[23] Pincus and Hoagland,[24] Cleghorn and Graham,[25] Lehmann et al,[26] and our own group.[27-29] Though definitive conclusions have not been reached, we have frequently noted that some schizophrenic patients not only fail to show an eosinopenia in response to the stimulus, but also, in some circumstances, evidence an eosinophilia.

Blood enzymes have been studied by Ashby,[30] Jones and Tod,[31] Richter and Lee,[32] and Early, Hemphill and Reiss,[33] but no conclusive findings have been reported. Macht[34,35] has extensively investigated and reported on the effect of blood sera from psychotic patients on seedling growth. He has found the sera from psychotic patients of all diagnostic categories exert toxic effects on seedlings.

PROCEDURE IN HEMATOSONOGRAPHY

In these two series, blood was drawn by venipuncture with an autoclaved, dry, sterile 19 or 20 gauge needle and a 20 or 10 cc. syringe. As soon as blood entered the syringe, the Brown-Honeywell Potentiometer was started, thus recording the beginning of the test run. (Point A on HSG curve.) The blood was drawn as rapidly as possible and was transferred immediately and directly to a chemically clean, dry 15 cc. conical centrifuge tube in which the ultrasound probe was set. The tube was suspended in a constant temperature water bath at 37° C. (±1°). Care was taken so that the entire probe and the lower part of the transducer were immersed in the blood specimen and the probe did not touch the tube. Approximately 12 cc. of blood was required.

After the first series was completed, a change in technique was made to enable utilization of only 9 c.c. of blood by lowering the probe into the tube. This modification resulted immediately in distinct differences in the curves. Critical values were not directly comparable with the tracings taken in the original series. As a result, the data were first studied as two separate series, each with patient and control groups. Upon analysis, it is seen that this constitutes a check of the accuracy of the procedure as against itself, insofar as the changes in technique produced two entirely discrete sets of data for both patients and controls.

These, and other observations, indicate the need for continual and accurate standardization of equipment, precautions against variations in current and in the electrical circuits, changes in the characteristics of the electronic tubes, changes in the probe, differences in procedure, and perhaps even including size of syringe and gauge of needles. Standardization of technique is imperative for we have reason to believe that seemingly minor alterations may also change some of the parameters being quantitated.

CLINICAL MATERIAL

A total of 73 hematosonographs (in two series, each with controls) have been analyzed—46 hospitalized and nonhospitalized patients and 27 nonpsychotic controls.

34 hospitalized patients: Of these, some were selected at random from a few of the wards in pavilions N, P, S and Reception of Creedmoor State Hospital, while others were selected at random from groups under special study by the research team. No particular criteria were used in selection beyond the presence of clinically demonstrable psychosis. Since the selection was made from specific wards in certain pavilions, the sampling is not typical of the total state hospital population.

12 nonhospitalized psychotics: In order to minimize the possible contributions of nutritional differences, a group of patients of the out-patient department of The Creedmoor Institute were tested. They were chosen at random from among out-patients who had previously been "worked-up" and diagnostically classified.

Diagnostic classification of the full patient population reveals:

	Hospitalized Psychotics	Nonhospitalized Psychotics	Total
Schizophrenia (Types)	(30)	(11)	(41)
Catatonic Type	18		18
Hebephrenic Type	3		3
Mixed Type	1		1
Paranoid Type	7	5	12
Simple Type		1	1
Unclassified	1	5	6
Manic-Depressive	(1)	( )	(1)
Depressed Type	1		1
Organic Psychosis	(2)	(1)	(3)
Cerebral Arteriosclerosis	1		1
Epidemic Encephalitis	1		1
General Paresis		1	1
Error in Classification	(1)		(1)
Control listed as patient	1		1
			46

Among the patients there were 2 adolescents and 1 mother of a schizophrenic child; 12 were under treatment or were receiving medication at the time of HSG test; 1 had received therapy up to within 4 days of HSG; 4 had had lobotomy or topectomy. Details as to age, sex, duration of hospitalization, number of previous admissions, as well as prior therapies and their results are recorded in the Summary of Data Table.

27 nonpsychotic controls: Apparently healthy members of The Institute and hospital staff were tested at random as "normals" for the establishment of comparative control data. These included 15 doctors and dentists, 4 nurses (3 female, 1 male), 2 psychologists, 1 attendant, 3 technicians (1 female), 2 administrative personnel. No selection of any kind was exercised beyond the fact that the individuals volunteered.

The hospitalized group of patients included 34 males and 0 females; the nonhospitalized psychotics, 8 males and 4 females; while the control group had 24 males and 4 females. The tests were run under conditions of good health, although in a few instances upper respiratory infections and menstruation were present. The tests of the controls were frequently interspersed with those of the patients in an attempt to approximate or equate for both groups such variables as temperature, time of day, relationship to meals, and season of the year.

A. CHARACTERISTICS AND NOMENCLATURE OF THE HEMATOSONOGRAPH (HSG)

The HSG, regardless of the blood sample used, has certain characteristic profiles (Fig. 1). In general, there is a short basal segment which is followed by a sharp rise; a shallow recession of moderate duration follows next, which is in turn succeeded by the major ascending segment of the curve.

In comparing these hematosonographs, it became apparent immediately that the characteristic segments described above, and certain of their attributes, are subject to quantitative variations. In order to make the direct comparisons between two or more hematosonographs necessary to evaluate a possible dichotomy, it was found desirable to utilize

a standardized system of notation for the various nodal points and segments of these curves. The nomenclature employed in this study is as follows:*

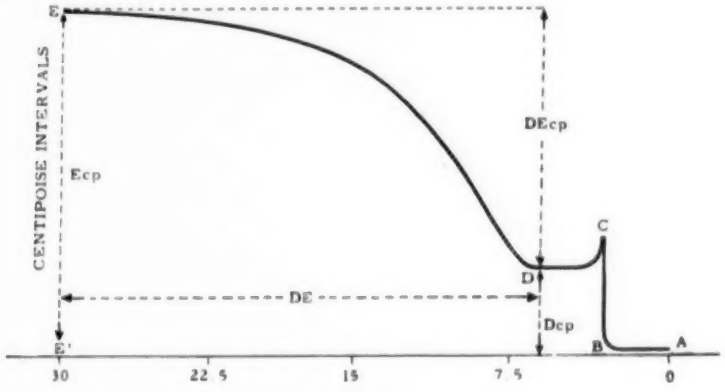

FIG. 1. Parameters and nomenclature of a stylized hematosonograph (HSG)—30 min.

AB	The preliminary basal portion of the HSG, prior to any ascent, measured in seconds.
Ccp	The height, from the preliminary basal portion to the peak of the primary node, measured in centipoise intervals (see Part I).
D	The departure point, or take-off point, for the major curve of the HSG.
Dcp	The height of the departure point, D, measured from the base line, in centipoise intervals.
CD	The interval, measured in seconds, from the nodal peak, C, to the departure point, D.
CDcp	The difference, measured in centipoise intervals, from the nodal peak, C, to the departure point, D.
E	The highest point attained by the HSG within 30 minutes. This is usually found at the 30 minute point, but in some instances occurs earlier (or later).
Ecp	The distance from the highest point, E, of the HSG, to the base line, measured in centipoise intervals.
DE	The interval, measured in seconds, from the departure point, D, to the highest point attained, E.
DEcp	The amount of climb from the departure point, D, to the highest point of the curve, E, measured in centipoise intervals.
DE/DEcp	The DE interval (measured in seconds) divided by DEcp (measured in centipoise intervals), resulting in an average rate of ascension of the

*Other nodal points and segments of the curve have been identified but are not included in this report inasmuch as they were not utilized in scoring. These additional points of the HSG curve have been noted in blood clotting studies extending over several hours.

curve, expressed as the average number of seconds required to ascend one centipoise interval.

Ecp Ccp The ratio of the maximum height, Ecp, to the primary nodal height, Ccp.

B. COMPARISON OF HEMATOSONOGRAPHS (HSG) OF PSYCHOTICS AND NONPSYCHOTICS

Using the technique described above, hematosonographs were made on the blood samples of the first series of 28 psychotic patients and 15 nonpsychotic controls. A second series of hematosonographs was made on the blood samples from another 18 patients and 12 more controls, but since these latter tests were run subsequent to the modifications in technique referred to above, the HSGs of this series are not directly comparable with those of series I and are therefore evaluated separately.

After extensive study of HSG factors, the conclusion was reached that seven factors or aspects of these curves could provide a possible composite measure of differentiation; that is, that collectively these variables might constitute a dichotomous quantitative differentiation (DQD) factor to discriminate between the blood samples of the psychotic patients and the nonpsychotic controls. These seven discrete variables are discussed below, comparison being made between patients and controls prior to the change in technique (designated Series I) and those tests made on patients and controls after the change (designated Series II). (Fig. 2 and 3.)

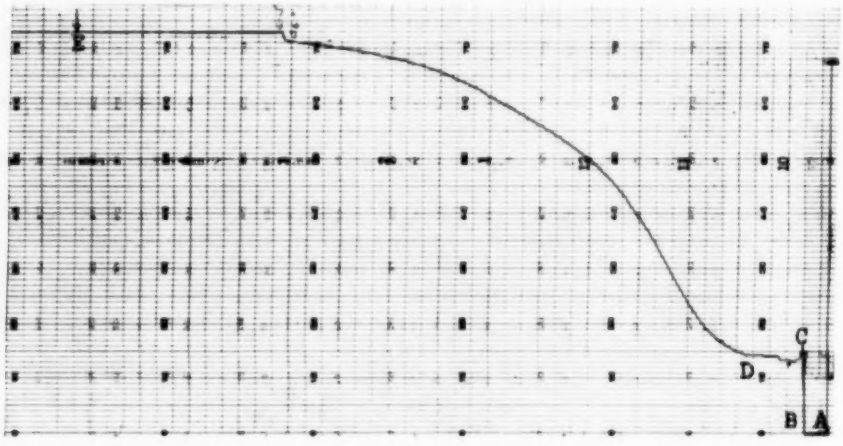

FIG. 2. CONTROL NO. CL20

	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
V	40	16	1720	75	59.75	13.5	4.56		No Psychosis
S	**	22.17	0	19.46	**	20.25	19.46	81.34	

** Factor not used in Series II.
v—Value as determined by measurement
s—Score as determined from table of weighted scores

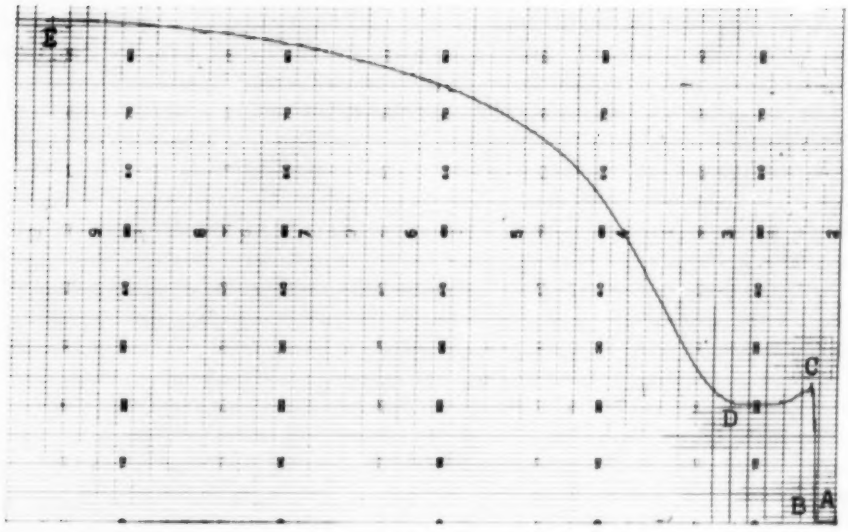

FIG. 3. PATIENT NO. 410

	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
V	40	24	1580	86	65.5	20.5	3.58		Psychosis
S	**	0	0	0	**	0	0	0	Untreated

Factor AB. Patients in Series I show an AB interval ranging from 20 to 140 seconds, while controls in this series have an AB variation of 20 to 80 seconds. Out of 28 patients, 20 (71.5 per cent) have an AB of 40 seconds or less, while 8 out of 15 controls (53.2 per cent) have an AB of 60 seconds or more. The chi-square test applied to these results shows a probability of slightly more than 10 chances in 100 that they might have arisen as a result of random sampling error or bias (chi-square = 2.56).

Series II patients have an AB range of 20-80, while Series II controls vary from 20 to 70. No difference of any statistical significance was found in the AB intervals of Series II patients as compared to Series II controls.

Factor Ccp. Series I patients have a Ccp range of 17-21.5 centipoise intervals, while controls in this series range from 13 to 33.5. No statistical significance attaches to the variations of patients as compared to controls in the measurement of Ccp in Series I.

Patients in Series II show a Ccp range of 15 to 27.5, a count of 19.5 or more being characteristic of 17 out of 18 patients (94.4 per cent), while Series II controls have a Ccp range of 14 to 25, with a count of 18.5 or less occurring in 9 out of 12 controls (75 per cent). The observed difference in Ccp measurements between patients and controls in this series is highly significant statistically, a chi-square of 15.6 indicating that the chances of these differences having arisen as a result of random sampling error are considerably less than 1 to 1000.

Factor DE. The DE interval range in Series I patients varies from 780 to 1760, and in Series I controls from 1160 to 1680. Of the patients, 22 out of 28 (78 per cent) have a DE interval of 1520 seconds or less, while in the controls 9 out of 15 (60 per cent) have a DE interval of 1560 or more. That these differences are so statistically significant is shown by a chi-square value of 6.4, indicating slightly more than 1 chance in 100 that they might have arisen as a result of random sampling errors.

The DE interval in Series II shows a somewhat similar degree of dichotomy. Patients in this series have a range of 1440 to 1720, while controls show a spread of 1200 to 1720. The DE interval is 1570 or more in 14 out of 18 patients (78 per cent), and is 1560 or less in seven out of 12 controls (58 per cent). The chi-square value of the association between these factor values and the subject's status relative to psychosis is 40.4, indicating that the observed differences show a probability of about 4 chances in 100 of having arisen as the result of random sampling errors.

Factor Ecp. The range of Ecp in Series I patients is 40.5 to 82, with 20 out of 28 patients (71 per cent) having an Ecp measurement of 71 or less. The Ecp range in Series I controls is from 63 to 81, with 11 out of 15 controls (73 per cent) having a value of 71.5 or more. The differences between patients and controls in the Ecp value are statistically significant, chi-square being 7.9, and the probability of the observed differences having arisen as a result of random sampling errors being less than 1 chance in 100.

The Ecp factor in Series II patients varies from 73.5 to 93, with 15 out of 18 patients (83 per cent) having a factor value of 76 or more. In Series II controls, the values range from 68 to 89.5, half of the controls having a measurement of 75 or less, the other half having a value of more than 76. There are approximately 5 chances in 100 that the observed differences might have arisen from random sampling errors, since a chi-square value of 3.8 is obtained from these data.

Factor DEcp. This factor in Series I patients varies from 21 to 62, with 21 out of 28 patients (75 per cent) having a measurement of 2.55 or less. In Series I controls the DEcp value ranges from 44.5 to 61, with 10 out of 15 controls (66 per cent) having a value of 53.5 or more. The observed differences in these measurements are statistically significant (chi-square is 7.09), the chances being less than 1 in 100 of their having arisen as the result of random sampling errors.

The DEcp factor in Series II patients and controls shows no statistically significant difference between these groups. Patients vary from 55.5 to 71, and controls range from 48.5 to 77.5, approximately as many patients falling at each end of the range as do controls.

Factor Dcp. Series I patients have a spread of 14 to 20.5 in their Dcp scores, while controls in this group are scarcely different with a range of 15.5 to 20. No difference of any statistical significance can be determined between the scores of patients and controls in this factor.

Series II patients have a Dcp range of 12 to 26 with 15 out of 18 (83 per cent) having a measurement of 18 or more. Controls of this series range from 12 to 21, but 9 out of 12 (75 per cent) have a value of 16 or less. A chi-square value of 10.3 confirms that the chances are much less than 1 in 100 of the observed variations having arisen as a result of random sampling errors.

Factor Ecp/Ccp. This factor shows a high degree of differentiation between the controls and patients of Series I. The patients range from 1.36 to 4.20, with 22 out of 28 (78 per cent) having a value of 3.55 or less. The controls show a range of 3.43 to 4.37, a value of 3.60 or more occurring in 12 out of 15 instances (80 per cent). Observed differences between controls and patients in this instance are highly significant statistically, chi-square = 13.77, the disparity between the results having a probability of considerably less than 1 chance in 1000 of having arisen as a result of random sampling errors.

In Series II patients the Ecp/Ccp values range from 2.75 to 5.06, with 14 out of 18 patients (77 per cent) having a value of 3.95 or less. The controls in this group vary from 3.32 to 5.32, with 9 out of 12 (75 per cent) having a score of 3.97 or more. A chi-square of 8.17, indicating a probability of less than 1 chance in 100 of the results having arisen as a result of random sampling errors, attests to the statistical significance of the observed differences.

C. HEMATOSONOGRAPHY OF OXALATED BLOOD AND PLASMA

The HSG curve of ovalated blood (Fig 4) appears similar to that of plain whole blood from point A to B to C and thence to D. Thereafter, however, the HSG of oxalated blood shows change in that its DE segment differs from the arc produced by whole blood described above. The DE segment of oxalated blood or plasma is a straight line with a slight upward inclination, indicating increasing viscosity and or effects of other physical changes (possibly sedimentation).

The addition of calcium to oxalated blood is followed by such changes that the curve then approximates that of unoxalated whole blood as it clots. This suggests that the DE

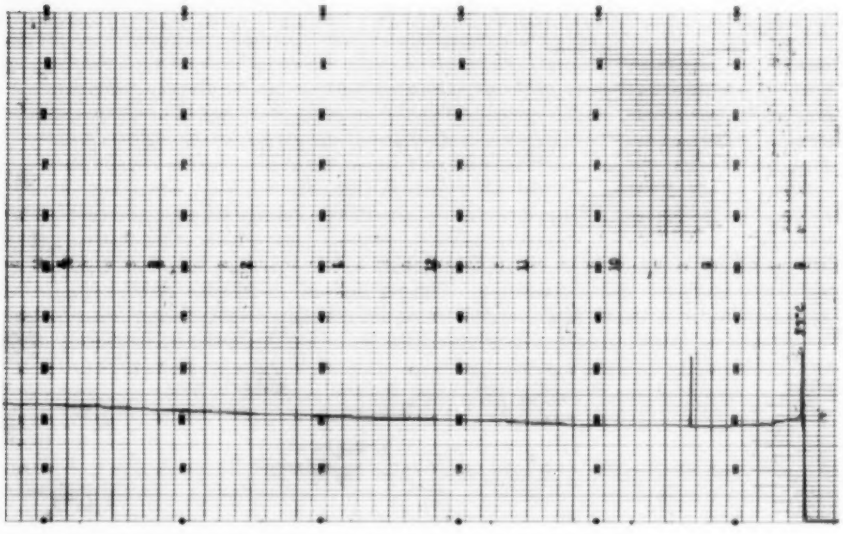

FIG. 4. HEMATOSONOGRAPH OF OXALATED BLOOD.

segment of whole blood reflects some physical change occurring in blood (presumably viscosity) associated with the process of clotting. Hematosonography thus permits more detailed observation and measurement of the changes occurring during clotting than any method hitherto available.

HSG studies of plasma reveal a DE segment similar to that of oxalated blood; again, the addition of calcium is followed by the development of a DE arc, another indication that hematosonography is recording changes associated with clotting.

Detailed studies are currently under way with plasma and oxalated blood, as well as concurrent investigations with Lee-White clotting time, prothrombin time, blood calcium, plasma proteins, and other parameters.

CONCLUSIONS

1. The use of ultrasound for quantitating purposes is termed ultrasonometry (USM).
2. The study of blood as it clots while exposed to ultrasound used as a quantitating mechanism and the autographic recording thus made is herewith designated hematosonography or hemosonography (HSG).
3. The graphs or curves recorded in hematosonography are termed hematosonographs or hemosonographs (HSG curves).
4. Hematosonography gives a "slow-moving picture" of changes (as yet undefined, possibly in viscosity and/or other factors) in certain physical characteristics of whole blood. This picture adds the dimensions of time and viscosity (and/or other factors) to the study of blood and its components.
5. The hematosonograph is completely quantitatable both in terms of time pattern and centipoises (or centipoise intervals—the square root of the centipoise measurement). In this respect it may differ from the interpretative aspects of EKG and EEG.
6. The HSG is a curve with definitive characteristics. Nodal points have been designated for ease of reference. The parameters of the curves and certain of their variational characteristics have also been elucidated.
7. The HSG as a quantitatable record of physical changes in blood affords a new approach not to one organ as the heart or the brain, but to the most complex and ubiquitous of all systems—the blood. Since all organs and tissues contribute to the composition of the blood, its parameters must in turn reflect some aspects of their function.
8. Since hematosonography enables quantitating in terms of physical characteristics as related to time pattern, it should be explored much as spectrophotometry and chromatography have been for potential applicability, not only to metabolic studies but to basic problems in chemistry as well.

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SUMMARY OF CLINICAL DATA OF PATIENTS SERIES I

PATIENT					PREVIOUS ADMISSIONS				PRESENT ADMISSION							
No.	Sex	Age	Diagnosis	Pavilion	No.	Duration in Days	Prior Therapy	Result	Duration to Date of HSG in Days	Prior Therapy	Result	Current Rx at Time of HSG	Elapsed Time Since 1st Adm. in Days	Total Cumulative Hospitalization in Days	Remarks	HSG Score
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
619	M	42	DP.C.	S	0	0	—	0	6055	Hydro ECT ECT ECT ECT	0 0 0 0 0	HT Placebo	6055	6055	—	0
603	M	27	DP.C.	S	1	124	Ins	‡	2680	ECT HT Pro-HT	0 0 0	None	3637	2804	—	0
625	M	23	DP.C.	S	1	1005	ECT Ins-ECT	0 ‡	355	—	0	None	1365	1347	—	0
231	M	36	DP.C.	N	0	0	—	0	1425	ECT Ins T/E	0 0 0	None	1425	1425	—	19.46
623	M	24	DP.C.	S	0	0	—	0	3070	Ins	‡	HT-Placebo	3070	3070	Acne	0
620	M	44	DP.C.	S	0	0	—	0	2368	—	0	HT Pro	2368	2368	—	0
211	M	47	DP.P.	P	1	436 2073	—	0	709	Preg T/E	0 0	None None	6205	3218	—	0
226	M	22	DP.C.	S	0	0	—	–	1013	Ins ECT Pent. Int. T/E T/E-Pro	0 0 0 † ¶C.S. Ret.	None	1013	1013	—	0
633	M	27	DP.C.	S	1	336	ECT, But	‡	3833	ECT	0	None	5375	4169	—	20.00
220	M	18	DP.H.	S	1 2	28 235	ECT	– · ·	698	T/E T/E T/E	0 0 †	None	1395	961	—	18.06
622	M	31	DP.C.	S	1	360	Ins	‡	3070	ECT	0	HT Pro	3650	3430	—	18.06

77	M	32	DP. GP.?	OPD	–	—	—	–	365	Pen HT	Therapy Incomplete	None	367	382	—	18.06
134	F	38	DP.P.	OPD	0	—	—	–	614	—	–	None	635	—	—	18.06
624	M	38	DP.C.	S	1	365+	Ins	‡	3285	ECT ECT	0 0	HT Placebo	4380	3650+	—	18.06
630	M	40	DP.P.	S	1	3	—	0	3847	ECT	0	None	4845	4556	—	18.06
75	M	61	DP.P.	OPD	1-H 3-OPD	121	ECT ECT Psycho-therapy	‡ 0 0	316	HT T/E ECT	‡	T/E	2555	121	—	20.00
85	M	16	DP.P.	OPD	0	0	—	–	183	T/E	‡	HT	356	356	—	20.00
627	M	30	DP.C.	S	1	1460	NO_2 Benz ECT	‡	745	ECT	0	None	2385	2205	—	20.00
168	F	33	DP.U.	H	3-H	90	ECT Ins	† †	26	—	–	None	34	90	Palp. Thyr; Trem; Tach;	20.00
165	F	33	DP.U.	OPD	1	181	P. Anal. Ins ECT	– – –	28	None	–	HT	664	88	—	20.00
140	F	39	DP.U.	H	0	0	—	–	172	None	–	HT	172	172	Ir. Men; BMR-O	21.94
138	M	32	DP.P.	H	1	150	—	–	190	None	–	HT	190	215	Fem. Contour Enl. Breasts Obesity	40.00
618	M	40	DP.C.	S	0	0	—	–	7665	ECT	0	HT Pro. Thi.	7665	7665*	1930 Palp. Thyr.	40.00
626	M	29	DP.C.	S	1	50	—	0	2920	ECT ECT ECT Top	0 0 0 0	None To go on HT	3650	2970	—	61.94
621	M	25	DP.C.	S	1	0	—	0	1095	ECT ECT ECT	0 0 0	HT Pro	2190	1825	—	61.94
616	M	43	DP.C.	S	0	0	—	0	8030	Met ECT ECT	0 0 0	HT Pro. Thi.	8030	8030	—	61.94
631	M	23	DP.M.	REC	0	20	—	–	39	None	0	None	59	59	—	80
221	M	19	DP.H.	S	0	0	—	–	1030	ECT-Ins T/E T/E T/E	0 0 0 0	None	1030	1030	—	100

SUMMARY OF CLINICAL DATA OF PATIENTS: SERIES II

PATIENT No.	Sex	Age	Diagnosis	Pavilion	PREVIOUS ADMISSIONS No.	Duration in Days	Prior Therapy	Result	PRESENT ADMISSION Duration to Date of HSG in Days	Prior Therapy	Result	Current Rx at Time of HSG	Elapsed Time Since 1st Adm. in Days	Total Cumulative Hospitalization in Days	Remarks	HSG Score
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
403	M	60	Psy. with Cer. Art.	N	0	0	—	–	1131	ECT Preg	0 0	None	1131	1131	—	0
602	M	17	Psy. with epid. enc.	S	1 2 3	100 3425 30	— — —	– – –	534	HT T/E-HT Pro-HT-T/E	0	None	4371	4089	—	0
507	M	51	DP.P.	N	1 2 3	66 50 2359	— — —	0	2916	None	0	None	5410	5391	—	0
508	M	44	DP.H.	N	1	375	—	–	8040 (7665)	None	0	None	8040	8040	—	0
410	M	65	DP.P.	N	3-4 5	? 1640	Ant —	0	1034	ECT Preg	0 0	None	6935	1674+	—	0
634	M	30	DP.P.	P	3	363	Ins Met	– ‡	2692	ECT Top	0	None	2920	2692	Homo	0
605	M	30	DP.P.	S	1 2	197 776	Ins Fev	(‡) ‡	1232	ECT Lob ECT HT Pro	† (‡) 0 0 0	None	2413	973	—	0
229	M	34	DP.C.	N	1	7	—	–	5220	T/E	0	None	5585	5227	—	18.06
V1A	M	51	DP.P.	OPD	0	—	—	–	680	ECT HT	¶	None	—	—	—	18.66
216	M	54	MD.D.	N	1	?	?	0	773	ECT Preg T/E	0 (‡) (‡)	None	3390	773	—	0
28	M	23	DP.S.	OPD	0	—	Glu	–	505	HT Pro	§	None	505	511	Moist extreme cold Obese	19.45
629	M	29	DP.C.	S	0	0	—	–	3675	Met ECT	† 0	None	3675	3675	—	19.46
231A	M	36	DP.C?	N	0	0	—	–	1425	ECT Ins T/E	0 0 0	None	1425	1425	—	0

652	M	30	DP.P.	S	0	0	—	—	3389	ECT Top	0 0	None	3389	3389	—	19.46
655	M	25	DP. Ment Defec.	REC	0	0	Ant-Pit Thyr ECT	†	15	None	0	None	2100	15	Hypo. Thyr. Cretin?Fro. Hypogonad.	20.25
147	M	17	DP.U.	H	0	—	—	—	177	None	0	HT	177	177	—	38.12
18	M	15	DP.U.	H	1-OPD	965	Group	Deteri-orated	544	HT-Pro T/E	§ §	Pro	1539	None	Cysts Hypogonad.	39.71
CL24**															—	61.87

EXPLANATION FOR SUMMARY OF CLINICAL DATA OF PATIENTS: SERIES I

Diagnosis (Column 4)
- DP.C.—Dementia Praecox Catatonic
- DP.H.—Dementia Praecox Hebephrenic
- DP.GP.—Dementia Praecox, General Paresis
- DP.P.—Dementia Praecox Paranoid
- DP.U.—Dementia Praecox Undetermined
- DP.S.—Dementia Praecox Simple
- DP.M.—Dementia Praecox Mixed

Therapy (Column 8, 11) Rx (Column 13)
- Ins—Insulin
- ECT—Electroconvulsive Therapy
- But—Butanol
- NO_2—Nitrogen oxide
- Benz—Benzedrine
- P.Anal.—Psychoanalysis
- Hydro.—Hydrotherapy
- HT—Histamine
- Pro—Proloid
- T/E—Testosterone with Estrogens
- Preg.—Pregnenolone
- Pent. Int.—Pentothal Intramuscular
- Pen—Penicillin

Result (Column 9)
- 0—Unimproved
- †—Slight improvement
- ‡—Some improvement
- *C.S.—Improved Convalescent status
- Ret.—Returned

Remarks (Column 16)
- Palp. Thyr.—Palpable Thyroid
- Trem.—Tremor, hands
- Tach.—Tachycardia
- Ir. Men.—Irregular menses
- BMR-O—Basal metabolism rate for obesity
- Fem.—Female
- Enl.—Enlarged

EXPLANATION FOR SUMMARY OF CLINICAL DATA OF PATIENTS: SERIES II

Diagnosis (Column 4)
- Psy. with Cer. Art.—Psychosis with cerebral arteriosclerosis
- DP.P.—Dementia praecox paranoid
- DP.H.—Dementia praecox hebephrenic
- DP.C.—Dementia praecox catatonic
- MD.D.—Manic depressive depressed
- DP.S.—Dementia praecox simple
- DP. Ment. Defec.—Dementia praecox (Mental Defective)
- DP.U.—Dementia praecox undetermin
- Psy. with epid. enc.—Psychosis with epidemic encephalitis
- CL24**—Control erroneously entered as patient

Therapy (Column 8) (Column 11) Rx (Column 13)
- Ant—Antuitrin
- Ins—Insulin
- Met—Metrazol
- Fev—Fever Therapy
- Glu—Glutamic Acid
- Top—Topectomy
- Thyr—Thyroid
- ECT—Electroconvulsive Therapy
- Preg—Pregnenolone
- HT—Histamine
- T/E—Testosterone with Estrogens
- Pro—Proloid
- Ant-Pit—Anterior pituitrin
- Lob—Lobotomy

Result (Column 9)
- ‡—Some improvement
- †—Slight improvement
- (‡)—Temporary improvement
- 0—No improvement
- §—Improvement
- *—Improvement

Remarks (Column 16)
- Homo.—Homosexual
- Hypo. Thyr.—Hypothyroid
- Hypogonad.—Hypogonadism
- Fro.—Froehlich's syndrome

Dichotomous Quantitative Differentiation (DQD) of Hematosonographs of Psychotics From Nonpsychotics*

PART III OF
QUANTITATED IDENTIFICATION OF PSYCHOSIS BY BLOOD SAMPLE

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Mathematical analysis of physical data from a blood sample identifies psychoses with a level of accuracy exceeding 85 per cent in 73 subjects (46 patients, mainly hospitalized and non-hospitalized schizophrenics and 27 nonpsychotic controls)—with a resultant chi-square of 31.77. Further differentiation between treated and untreated psychotic patients is also attained with an accuracy in excess of 80 per cent and a chi-square of 10.57.

The relationship of metabolic factors to psychiatric processes is revealed in much of our physiologic findings[1-4] and has been discussed to some extent in our report—Physiodynamics of Major Metabolic Disorders.[5,6] Our research flow chart, originally projected in 1948, while devoted fundamentally to psychiatric investigation, has, for several years, suggested areas of investigation not only in endocrinology but also in other metabolic deviations: in surgery, as in the treatment of burns; in obstetrics and gynecology, as in possible new tests for pregnancy; and in internal medicine, as in certain complications of diabetic ketosis. Unless one has experienced such findings, which relate clinical entities to fundamental biological processes, it can come as something of a shock that two pure physical sciences, physics and mathematics, can by themselves enable differentiation of a psychotic from a nonpsychotic simply on the basis of a blood specimen. Conversely, as can be seen, the demonstration of such a fact can afford, in a measure, significant counterproof—to borrow a word from Claude Bernard—of the great import of pathophysiologic factors, particularly neuroendocrine, in the bodily processes associated with psychoses.

OBJECTIVES

The present investigation sought:

1) to apply the quantitated critical factors obtained by hematosonography so as to determine whether a dichotomous quantitated differentiation (DQD) exists between psychotics and nonpsychotics;
2) to determine the statistical significance of such findings.

*Reprinted from J. Clin. Exp. Psycho. *12*:304-319, Oct.-Dec. 1951.

RESULTS

Dichotomous Quantitative Differentiation (DQD) of Hematosonographs of Psychotics

It will be observed from comparison of the hematosonographs of psychotics and nonpsychotics, analyzed in the preceding paper, that a differential exists in the relative dichotomization of these curves when any single factor is compared with another. For example, in Series I the Ccp factor is not usable for the dichotomous quantitative differentiation of these HSG curves whereas in Series II the Ccp factor is an extremely useful variable, correctly identifying 26 out of 30 hematosonographs as to their psychotic or nonpsychotic origin. The variation in predictive value of the several factors in one series as compared to another arises from the gross qualitative changes induced in the hematosonographs as a result of modification of technique. Thus, in order to assay the dichotomous differentiating ability of the hematosonographs for the tests run before and after change in technique, those factors which show the highest indication of prediction for each series have been selected.

In the case of Series I patients and controls, the factors used to determine the possible dichotomy of psychotic as compared to nonpsychotic were AB, DE, Ecp, DEcp, and Ecp/Ccp. Each of these factors was assigned a scoring weight according to its proportional contribution to the total obtained differentiation of the two types of hematosonographs.* Thus, the following scoring weights were employed:

Factor	*Weight*
AB	18.06
DE	20.00
Ecp	20.00
DEcp	20.00
Ecp/Ccp	21.94

The process of actual dichotomization of the HSG curves of patients and controls proceeded as follows: for each factor the actual value observed on the curve was recorded; if the value fell within the observed critical range of controls (i.e., that range which includes the majority of controls), the factor value was given a scoring weight accord-

*The method of weighting each factor for its contribution to the total score is predicated upon the degree of dichotomy shown by the individual factor relative to all the factors used. This method is best illustrated by a hypothetical example wherein we may designate three factors respectively as X,Y,Z. Let us assume that factor X correctly identifies 75 per cent of our subjects as to psychotic or nonpsychotic. Let us then make the further assumptions that factor Y correctly identifies 80 per cent of our subjects, and that factor Z correctly identifies 85 per cent of our subjects. We then add these percentages of identification (75 per cent + 80 per cent + 85 per cent) and obtain a total of 240. The contribution which each of the factors, X, Y, Z, has made to the total 240 then becomes the scoring weight for the respective factor. Thus, factor X with a 75 per cent identification contributes 31.25 per cent of the total weight and is therefore given a scoring weight of 31.25; factor Y has a contributory value of 33.33 per cent to the total 240 and is therefore accorded a scoring weight of 33.33; finally, factor Z is found to contribute 35.42 per cent of the total of 240 and is thus accorded a scoring weight of 35.42.

ing to the protocol above.* The weighted scores were then added, and if the total was 50 or less, the HSG was considered to be that of a psychotic patient; if the total weighted score was 51 or more, the HSG was identified for the purpose of this test as being that of a nonpsychotic control.

Results of the foregoing method of testing the dichotomous differentiating ability of the hematosonographs of Series I patients and controls are seen in the following protocol:

	SCORE		
Series I	<50	51>	Number
Patients	23	5	28
Controls	4	11	15
	27	16	43

The above protocol indicates that 79 per cent of the subjects in Series I are identifiable as to a psychotic or nonpsychotic state on the basis of their hematosonographs. That the observed dichotomy is highly significant statistically is attested by a chi-square value of 12.86, indicating the probability of considerably less than 1 chance in 1000 that these differences arise from random sampling errors.

* The method of scoring the individual hematosonograph is predicated upon the values of the specific factors and the weighted score accorded each such factor.

In Series I the combination of the following five factors was found to produce a high degree of dichotomy between patients and controls: AB, DE, Ecp, DEcp, and Ecp/Ccp. For example, upon inspection of our data we find that factor Ecp/BC correctly identifies 72 per cent of our subjects according to whether the Ecp/Ccp value is 71 or less (patients) or 71.5 or more (controls). Since as shown in our protocol, factor Ecp/Ccp in Series I carries a scoring weight of 21.94 we accord this score whenever the Ecp/Ccp value is 71.5 or more. If the Ecp/Ccp value is less than 71.5 the subject receives a score of zero for this particular factor.

Using the foregoing method, we score Series I subjects as follows:

Factor	*Critical Value*	*Score*
AB	60 or more	18.06
DE	1560 or more	20.00
Ecp	71.5 or more	20.00
DEcp	53 or more	20.00
Ecp/Ccp	3.6 or more	21.94

If the total score is 50 or less, the subject is identified as a patient; if the total score is 51 or more, the subject is identified as a control.

The same method is used for scoring Series II subjects, but with different factors and weights:

Factor	*Critical Value*	*Score*
Ccp	18.5 or less	22.17
DE	1560 or less	18.66
Ecp	75 or less	19.46
Dcp	16 or less	20.25
Ecp/Ccp	3.97 or more	19.46

As with Series I subjects, a total score of 50 or less is considered to identify a patient, while a total score of 51 or more is used to identify a control.

The same system of testing dichotomy and method of weighting was used for the subjects of Series II. In this instance, the factors used and their relative scoring weights were as follows:

Factor	*Weight*
Ccp	22.17
DE	18.66
Ecp	19.46
Dcp	20.25
Ecp/Ccp	19.46

The results of this test of dichotomy in Series II patients and controls are set forth in the following protocol:

	SCORE		
Series II	<50	51>	Number
Patients	17	1	18
Controls	2	10	12
	19	11	30

The dichotomous ability of the hematosonograph in differentiating between psychotic and nonpsychotic blood in the case of the Series II subjects is well shown in these data. The results have a high degree of significance, chi-square being 18.75.

A comparison of Series I patient scores with Series II patient scores shows a somewhat higher score trend in Series I patients, half of the group of 28 having a score of 20 or more, the other half having a score of less than 20; Series II patients as a result of slightly different weights being used, largely have scores of less than 20, since 14 out of 18 scores were less than 20. However, these differences are statistically not significant and arise as a result of sample error, since a chi-square value of 3.55 is obtained in testing the association of score between Series I and II. The difference between the scores of Series I controls as compared to Series II controls is even smaller, since virtually an even split occurs in the scores of these two groups. Controls of Series I have a score of 81.34 or more in 6 out of 12 cases, while controls of Series II have a score of 78 or less in 8 out of 15 cases. A chi-square value of 0.02 confirms the fact that the observed minor difference is almost certainly (90 chances out or 100) due to sampling error and therefore statistically validates pooling of the two control samples.

The foregoing comparisons of controls and patients in both groups indicate the validity of considering patients of both groups as insignificantly differentiated from each other, while controls may similarly be regarded as homogeneous so far as their hematosonographic scores are concerned. The question remains as to whether the pooled patient sample is significantly dichotomized from the pooled control sample. The following protocol shows the direct comparison of all patient scores with all control scores:

	SCORE		
	<50	51>	Number
Patients	40	6	46
Controls	6	21	27
Total	46	27	73

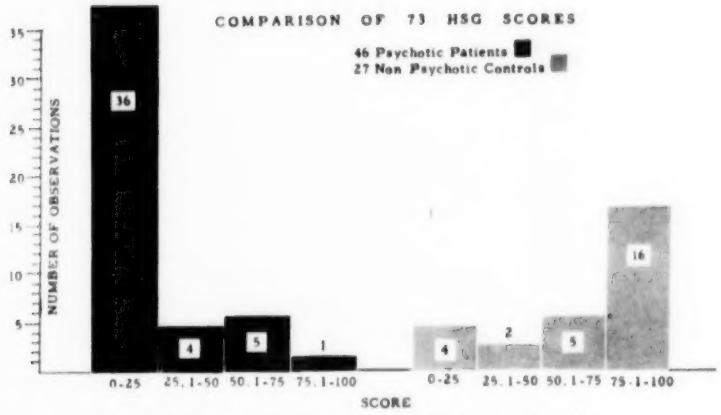

FIG. 1. Dichotomous Differentiation of Psychotic Patients from Controls = 83.5%; $x^2 = 31.77$

As indicated in the above protocol, 61 out of 73 subjects (83.5 per cent for whom hematosonographs were taken and scored, can be correctly identified as psychotic or non-psychotic on the basis of their hematosonographic scores. The observed differentiation on the basis of the hematosonographic scoring is strongly significant, the results showing a chi-square value of 31.77 and consequently being a certainty for all practical purposes of an origin independent of sampling errors.

In reviewing the data on the 6 psychotic patients whose scores fall within the normal range of the controls, we find that 3 were on medication at the time of the test (histamine, thyroid and/or propylthiouracil).

Review of the data on the 6 controls whose scores fall below the normal range, reveals the possibility that upper respiratory infection and menstruation may cause significant deviation in the HSG score, since 3 of the 6 were either menstruating and/or with a cold.

Hematosonographic Comparison of Treated and Untreated Psychotics

As one observed the sharpness of the dichotomization between patients and controls (Fig. 1), it becomes evident that:

a) the samples used are highly representative of their respective populations;

b) there were "contaminants" which could yield findings of great significance.

In graphing untreated psychotics vs. control nonpsychotics, one finds the dichotomization still more clearly apparent. (Fig. 2.)

Analysis of these two groups reveals a DQD in excess of 88 per cent and a chi-square of 36.04, indicating much less than 1 chance in 1000 of the observed differentiation having arisen as a result of random sampling errors.

Examination of the HSG scores of all 46 psychotic patients studied during the course of the present investigation shows an important and significant dichotomy between the

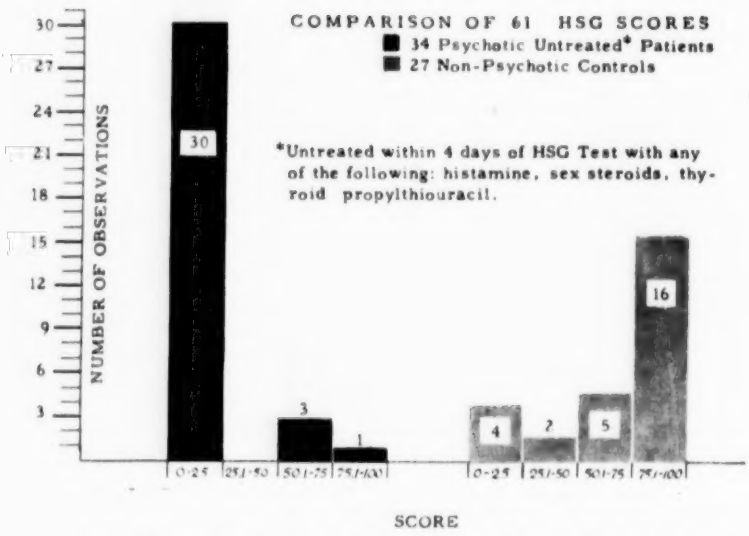

FIG. 2. Dichotomous Quantitative Differentiation of Untreated Patients from Controls = 88.5%; $x^2 = 36.04$.

scores of patients treated or receiving certain medication within four days of the time of their HSG test, and those patients who were completely untreated or who had been treated or administered certain medications more than four days prior to their HSG test. (As used here, the term "treatment" refers to administration of any of the following: Proloid, sex steroids, histamine, propylthiouracil).

In 34 untreated patients, the HSG scores range from 0 to 100, with 30 patients having scores of 20.25 or less. In 12 treated patients, the HSG scores vary from 0 to 61.9, with 7 out of 12 patients having scores of 21.94 or more. Hence, 37 out of 46 patients (80.4 per cent) can be identified as to whether or not they were administered certain medications within four days prior to the HSG test. This dichotomous quantitative differentiation is highly significant, since the chi-square yields a value of 10.57 indicating that the probabilities are only about 1 in 1000 that the observed dichotomy could have arisen as a result of the random sampling errors.

DISCUSSION

1. *As to what Hematosonography measures*:

At this writing it should be stressed that the biologic elements which HSG measures are not yet fully elucidated. It would appear as though the HSG measures dynamic physical changes in whole blood during the clotting process. What influence ultrasound itself exerts on the blood remains to be determined. That the HSG offers a moving profile of the effects of biochemical substances on the clotting process and that this method may be applicable to the study of many metabolic problems is only suggested and remains to be proved. That these leads must be investigated is indicated by the

data we have presented. Conclusions as to how broad an applicability hematosonography may have should be reserved pending the accumulation of large experience in many biologic fields. That hematosonography may be an important scientific technique for biologic quantitation has been demonstrated by our data. We cannot, however, overstress the need for restarint and caution in respect to any new development. Needless to say, our studies on hematosonography are going forward on a number of fronts in relation to its fundamental medical and biochemical applicability.

2. *As to standardization of procedures and calibration of equipment for Hematosonography*:

   Our experience has indicated that care and control are essential to the accuracy of the procedure. Seemingly trivial or seemingly unrelated changes can lead to confusing results and may lead to the necessity of re-evaluation of factor variation.

3. *As to the accuracy of Hematosonography*:

   It must be stressed that for this series 83.3 per cent accuracy is a minimal figure because—

   a. the test was weighted against itself since the critical breakover points for the factors were raised by the higher scores of most of the treated patients. This also weights the test more against the controls than against the patients;

   b. no correcting factor for certain therapies was used to adjust for what has been demonstrated to be its deviating effect upon the score;

   c. menstruation and upper respiratory infection were neither ruled out in the controls nor corrected for in the scoring; the data suggest that these conditions affect the scores.

4. *As to what Hematosonography does*:

   At this juncture we would like to stress that the test does not give a clinical diagnosis. It has afforded a dichotomous quantitative differentiation of psychotic from nonpsychotic, and also of treated from untreated psychotic in the two series studied. This DQD has a high order of accuracy and a very high order of statistical significance.

   The dichotomy between treated and untreated patients is very important for—

   a. it lends support to the validity of the procedure used in scoring, since the original value weight and scores were set for dichotomization between patients and controls. When this same method was used as a means of identifying treated or untreated patients, it was found to be highly accurate.

   b. it points to a common biophysical effect produced by thyroid, testosterone, histamine, and propylthiouracil. This is interesting in the light of a previous report which discussed physiologic common denominators of various therapies employed in psychiatry. Further study may elicit whether the ability to raise the HSG score is common to all the therapies currently utilized and whether there is an association between clinical improvement and attainment of a score which approaches or falls into the normal ranges. The conclusive demonstration of such association could provide psychiatry with a truly objective means of evaluating therapies.

   c. it emphasizes again the importance of maintenance of therapy for psychoses which are in the main truly chronic diseases. If the biophysical effects of therapy are not elicited when medication had been discontinued 4 days prior to testing, one may assume that some of these effects are in all likelihood transient. In order to maintain

whatever beneficial attributes they may have, it may become necessary in many instances to continue therapy over extremely long periods. Clinical observations had led this group to similar conclusions previously.

It may be of interest to record at this point that a survey of 1505 consecutive necropsies performed at Creedmoor State Hospital (1932 to 1949) revealed the following:

2 prostatic carcinoma
3 prostatic fibrosis
2 prostatic hyperplasia
12 breast carcinoma

Of these, none occurred among the 236 schizophrenics autopsied. Carcinoma of the breast was found in 1 involutional melancholic. The importance of this is emphasized by the fact that the schizophrenias constituted approximately 40 per cent of the hospital population in the years above mentioned. This may be more than passing interest, for if schizophrenia is the result of hormonal dysequilibrations characterized by adrenocortical operative excess and hypogonadal and or hypothyroid (etc.) operative deficiency (as was postulated in 1949 when the psychosis-producing effects of cortisone were predicted[5,6]), then one would not expect to find metabolic diseases which are not associated with such hormonal imbalances. As an illustration, it has been shown[7] that the urine of schizophrenic males more closely approximates in its hormonal concentrations the urine of a normal female than that of a male. Thus the usual incidence of prostatic carcinoma would not be expected in the schizophrenias. Similarly, if female schizophrenics have a relative adrenocortical and androgenic operative excess (viz. marked hirsutism) or a relative estrogenic operative deficiency, then breast carcinoma would not be likely to occur in the same frequency as in the general population. Since the HSG scores seem to be influenced by hormonal forces as revealed during medication, it would seem to follow that hematosonography may be informative when applied to blood studies of patients with prostatic and breast carcinoma.

In regard to the general problem of blood clotting and *in vivo* clotting as in coronary thrombosis and occlusion, it may be noted that the survey (referred to above) recorded 13 cases of coronary pathology. Of these, none occurred in schizophrenics. The ability to study more accurately the clotting process as afforded by HSG may also permit the elucidation of the metabolic factors underlying the dissociation of coronary thrombosis and schizophrenia.

At the First International Congress of Psychiatry meeting in Paris last year, we stated[8] that "We are today on the threshold of the era of metabolic medicine and metabolic psychiatry. This metabolic era is as full of promise as the concurrently developing atomic era is fraught with dangers. Through the metabolic era psychiatry will come to its fullest understanding of neuronal physiology and its relationship to psychodynamics. Predictability and control will become fundamental to a science of psychiatry in which modern physics, chemistry, and mathematics will be fused into a newer knowledge of the energetics and integration of the nervous system whose bizarre symptomatologic manifestations have fascinated and victimized man from time immemorial." Our physiologic findings had led us inexorably to such conclusions. Yet, it was evident from the diffi-

culties we had encountered that methods of precise quantitation are essential. We are grateful for the privilege of presenting one such, which we hope will help carry us over the threshold into the era of "metabolic medicine" and "metabolic psychiatry."

SUMMARY

A. Investigation of the whole blood of 34 hospitalized and 12 nonhospitalized, treated and untreated psychotics and 27 controls have been carried out utilizing ultrasound as a quantitating modality of certain, as yet undefined, physical characteristics of clotting blood.
   1. A difference between the hematosonographs (HSG) of psychotics and nonpsychotics, as a group, has been demonstrated with a chi-square of 30.59.
   2. A difference between the HSG scores of 34 untreated psychotics and of 12 treated psychotics has also been demonstrated with a chi-square of 10.57.

B. Following a factor analysis and properly weighted scores (without using correcting factors for therapy, menstruation, or upper respiratory infection), it is possible by dichotomous quantitated differentition (DQD):
   1. to discriminate between patients and controls with an accuracy of 83.5 per cent.
   2. correctly to identify patients as such with an accuracy of 87 per cent.
   3. correctly to identify whether or not the patient is receiving certain medications with an accuracy of 80.4 per cent.

C. The scores of patients who either were receiving or had, within 4 days of testing, received such substances as histamine, sex steroids, thyroid, and propylthiouracil, and that of one patient 9 months after lobotomy were either higher and closer to the normal scores or actually scored within the control range. It may be of some significance that 3 out of 6 of the failures in identification were patients receiving these medications.

D. Hematosonography is *not*, in this report, presented as a perfected and absolute diagnostic technique in psychiatry. Endocrine disturbances such as frank hypothyroidism or hypogonadism or other biochemical disturbances might conceivably affect the accuracy of the HSG score in the differentiation of psychotics from nonpsychotics. This very consideration simultaneously suggests the potentialities of this new tool in the study of endocrine function, endocrinopathies, and other metabolic disorders as they are reflected through their influence upon blood clot behavior. The applicability of hematosonography for the observation and control of the effects of hormonal, metabolic, and other therapies is foreseeable.

CONCLUSIONS

These investigations have demonstrated:

1. The applicability of ultrasound in a new type of blood study—hematosonography (HSG).
2. The use of HSG to differentiate, with a high degree of accuracy (over 83 per cent) and statistical significance (chi-square of 30.59), psychotics from nonpsychotics by ultrasonic investigation of a blood sample. Thus, HSG
   a. has demonstrated a definitive biologic difference between psychotics and nonpsychotics;

b. has afforded a measure for quantitating this difference, and

c. is incorporating elements of the basic sciences of physics and mathematics into the methodology of psychiatric research.

3. Hematosonography has further differentiated, with high accuracy (over 80 per cent) and statistical significance (chi-square of 10.57), psychotics receiving histamine, thyroid, propylthiouracil, and sex steroids from not receiving these therapies. Thus,

a. HSG supports previous evidences of common denominators in some of the therapies used in the psychoses; in this instance, elevated HSG scores are common to patients receiving these therapies.

b. in recording differences in patients receiving such substances, the HSG may, if further investigations are supportive, afford a valuable index to hormone and possibly other therapies.

c. by differentiating patients who were receiving therapy at the time of HSG from those who had not or who had received therapy up to four days prior to HSG, the procedure suggests that therapy must be maintained. The finding of elevated HSG scores (toward or into the normal range) in psychotic patients undergoing certain therapies points to physiological effects of these therapies which may eventually help correlate therapy and the results of therapy by affording objective criteria and indices.

4. The implications of hematosonography are so far-reaching in endocrinology and metabolic fields as well as in other branches of medicine, biology, and chemistry that extensive exploration of this new acquisition of medical science is indicated.

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PROTOCOL OF FACTOR VALUES AND SCORING OF PATIENTS: SERIES I

Patient No.	Factor Value & Score	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
1	2	3	4	5	6	7	8	9	10	11
619	v	40	21	1500	71	52.5	18	3.45		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
603	v	40	18	1500	40.5	24	17	2.02		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
625	v	40	18.5	1480	56.5	39.5	17	2.98		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
231	v	40	20	1300	64	38.5	18	3.12		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
623	v	40	19	1280	66	41.5	17.5	3.47		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
620	v	40	21	1360	70.5	52.5	18	3.36		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated‡
211	v	40	18.5	1480	64	47.5	16.5	3.28		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
226	v	40	19.5	920	60.5	43	15.5	3.10		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
633	v	40	21	820	57	36	20	2.72		Psychosis
	s	0	*	0	0	0	*	0	0	Untreated
220	v	60	20	840	56.5	33	15.5	2.90		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated
622	v	140	33.5	980	68	37.5	19.5	1.36		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated‡
77	v	60	15.5	1480	54	48	14	3.48		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated
134	v	80	13	780	46	21	15	2.56		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated
624	v	60	18	980	59.5	32	15.5	3.30		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated
630	v	60	17	1280	64	46.5	15.5	3.55		Psychosis
	s	18.06	*	0	0	0	*	0	18.06	Untreated
75	v	40	24	1760	66.5	45.5	20.5	2.76		Psychosis
	s	0	*	20	0	0	*	0	20	Untreated‡

PROTOCOL OF FACTOR VALUES AND SCORING OF PATIENTS: SERIES I

Patient No.	Factor Value & Score	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
1	2	3	4	5	6	7	8	9	10	11
85	v	40	22	1560	71	51.5	19.5	3.22		Psychosis
	s	0	*	20	0	0	*	0	20	Untreated‡
627	v	40	22	1620	70.5	51	19.5	3.20		Psychosis
	s	0	*	20	0	0	*	0	20	Untreated
168	v	20	24	1120	74.5	49	20	3.10		Psychosis
	s	0	*	0	20	0	*	0	20	Untreated
165	v	20	22	1680	69	48.5	20.5	3.14		Psychosis
	s	0	*	20	0	0	*	0	20	Untreated‡
140	v	20	18	1280	65	46.5	16.5	3.60		Psychosis
	s	0	*	0	0	0	*	21.94	21.94	Treated
138	v	40	20	1740	82	62	20	3.10		Psychosis
	s	0	*	20	20	0	*	0	40	Treated
618	v	40	22	1520	76	56.5	20.5	3.46		Psychosis
	s	0	*	0	20	0	*	0	40	Treated
626	v	40	19	1420	77	56.5	17.5	4.05		No Psychosis†
	s	0	*	0	20	20	*	21.94	61.94	—‡§
621	v	40	18.5	1280	73	56	17	3.74		No Psychosis†
	s	0	*	0	20	20	*	21.94	61.94	—
616	v	40	19.5	1520	80	61.5	18	4.10		No Psychosis†
	s	0	*	0	20	20	*	21.94	61.94	—
631	v	80	17.5	1520	73.5	57	16.5	4.20		No Psychosis†
	s	18.06	*	0	20	20	*	21.94	80	—‡
221	v	60	19	1620	72	54	18	3.78		No Psychosis†
	s	18.06	*	20	20	20	*	21.94	100	—‡

PROTOCOL OF FACTOR VALUES AND SCORING OF CONTROLS: SERIES I

Control No.	Factor Value & Score	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
1	2	3	4	5	6	7	8	9	10	11
CL1	v	40	18.5	1660	66	48.5	17.5	3.47		Psychosis†
	s	0	*	20	0	0	*	0	20	—
CL2	v	80	18	1400	66	48.5	16	3.67		Psychosis†
	s	18.06	*	0	0	0	*	21.94	40	U.R.I.
CL3	v	60	17	1160	63	44.5	15.5	3.70		Psychosis†
F	s	18.06	*	0	0	0	*	21.94	40	Menses
CL4	v	80	17	1280	67	49	15.5	3.94		Psychosis†
F	s	18.06	*	0	0	0	*	21.94	40	U.R.I.
CL5A	v	60	18	1360	72	52.5	16.5	4.00		No Psychosis
	s	18.06	*	0	20	0	*	21.94	60	U.R.I.
CL2A	v	40	21	1560	71.5	54.5	17	3.48		No Psychosis
	s	0	*	20	20	20	*	0	60	
CL6	v	20	21.5	1460	78.5	59	19.5	3.64		No Psychosis
F	s	0	*	0	20	20	*	21.94	61.94	
CL7	v	60	21	1640	74	55	19	3.43		No Psychosis
	s	18.06	*	20	20	20	*	0	78.06	
CL8	v	60	20.5	1400	75.5	53.5	17.5	3.78		No Psychosis
	s	18.06	*	0	20	20	*	21.94	80	U.R.I.
CL9	v	40	20.5	1640	78.5	60.5	18	3.83		No Psychosis
	s	0	*	20	20	20	*	21.94	81.94	
CL5	v	40	18	1620	75.5	58.5	17	4.20		No Psychosis
	s	0	*	20	20	20	*	21.94	81.94	
CL8A	v	40	17	1560	74.5	58.5	16	4.37		No Psychosis
	s	0	*	20	20	20	*	21.94	81.94	
CL10	v	20	20.5	1620	73	53.5	19.5	3.60		No Psychosis
F	s	0	*	20	20	20	*	21.94	81.94	
CL11	v	60	20	1680	81	61	20	3.85		No Psychosis
	s	18.06	*	20	20	20	*	21.94	100	
CL12	v	60	19.5	1560	75	58.5	16.5	3.75		No Psychosis
	s	18.06	*	20	20	20	*	21.94	100	

EXPLANATION FOR SERIES I

v—Value as determined by measurement
s—Score as determined from table of weighted scores
*—This factor not used in scoring Series I.
†—Interpretation of clinical status incorrect
‡—Interpretation of therapy status incorrect
§—Topectomy
U.R.I.—Upper respiratory infection. F—Female.

PROTOCOL OF FACTOR VALUES AND SCORING OF PATIENTS: SERIES II

Patient No.	Factor Value & Score	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
1	2	3	4	5	6	7	8	9	10	11
403	v	30	22.2	1710	83	62	21	3.73		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated
602	v	30	22.5	1570	79	59	20	3.51		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated
507	v	30	27.5	1710	83	58.5	24.5	3.01		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated
508	v	30	24	1720	84.5	63	21.5	3.52		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated
410	v	40	24	1580	86	65.5	20.5	3.58		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated
634	v	20	22.5	1700	86	65.5	20.5	3.82		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated§
605	v	20	27	1590	84	58	26	3.11		Psychosis
	s	**	0	0	0	**	0	0	0	Untreated¶
229	v	30	20	1510	77	58	19	3.85		Psychosis
	s	**	0	18.66	0	**	0	0	18.66	Untreated
V1A	v	70	20	1560	79	60	19	3.95		Psychosis
	s	**	0	18.66	0	**	0	0	18.66	Untreated
216	v	40	20	1440	77	58	19	3.85		Psychosis
	s	**	0	18.66	0	**	0	0	18.66	Untreated
28	v	80	21	1620	68.5	48.5	20	3.26		Psychosis
	s	**	0	0	19.46	**	0	0	19.46	Untreated
629	v	20	21.5	1590	93	71	22	4.32		Psychosis
	s	**	0	0	0	**	0	19.46	19.46	Untreated
231A	v	30	21	1700	87.5	68	19.5	4.16		Psychosis
	s	**	0	0	0	**	0	19.46	19.46	Untreated
632	v	20	22.5	1700	91	71	20	4.04		Psychosis
	s	**	0	0	0	**	0	19.46	19.46	Untreated§
635	v	40	22	1640	79	67	12	3.59		Psychosis
	s	**	0	0	0	**	20.25	0	20.25	Untreated
147	v	40	26.7	1520	73.5	55.5	18	2.75		Psychosis
	s	**	0	18.66	19.46	**	0	0	38.12	Treated
18	v	30	19.5	1570	74	62	12	3.79		Psychosis
	s	**	0	0	19.46	**	20.25	0	39.71	Treated
CL2a	v	25	15	1720	76	62.5	13.5	5.06		Psychosis†
	s	**	22.17	0	0	**	20.25	19.46	61.88	—

PROTOCOL OF FACTOR VALUES AND SCORING OF CONTROLS: SERIES II

Control No.	Factor Value & Score	AB	Ccp	DE	Ecp	DEcp	Dcp	Ecp/Ccp	Total Score	Interpretation
1	2	3	4	5	6	7	8	9	10	11
CL13	v	60	25	1490	83	63.5	19.5	3.32		Psychosis‡
	s	**	0	18.66	0	**	0	0	18.66	
CL14	v	30	21.5	1200	81.5	61.5	20	3.79		Psychosis‡
	s	**	0	18.66	0	**	0	0	18.66	
CL15	v	30	17.5	1680	89.5	77.5	12	5.11		No Psychosis
	s	**	22.17	0	0	**	20.25	19.46	61.88	
CL2B	v	30	14	1420	48.2	36.7	11.5	3.44		No Psychosis
	s	**	22.17	18.66	19.46	**	20.25	0	80.54	
CL16	v	40	17.5	1440	81	63.5	13.5	4.62		No Psychosis
	s	**	22.17	18.66	0	**	20.25	19.46	80.54	
CL17	v	20	17.5	1560	83	68	15	4.74		No Psychosis
	s	**	22.17	18.66	0	**	20.25	19.46	80.54	
CL18	v	30	14	1600	74.5	62	12.5	5.32		No Psychosis
	s	**	22.17	0	19.46	**	20.25	19.46	81.34	
CL19	v	50	18.5	1570	73.5	61.5	12	3.97		No Psychosis
	s	**	22.17	0	19.46	**	20.25	19.46	81.34	
CL20	v	40	16	1720	73	59.75	13.5	4.56		No Psychosis
	s	**	22.17	0	19.46	**	20.25	19.46	81.34	
CL21	v	30	15	1550	68	55	13	4.53		No Psychosis
	s	**	22.17	18.66	19.46	**	20.25	19.46	100.0	
CL22	v	40	17	1510	69	55	14	4.05		No Psychosis
	s	**	22.17	18.66	19.46	**	20.25	19.46	100.0	
CL23	v	30	15.5	1530	75	59	16	4.83		No Psychosis
	s	**	22.17	18.66	19.46	**	20.25	19.46	100.0	

EXPLANATION FOR SERIES II

v—Value as determined by measurement
s—Score as determined from table of weighted scores
**—This factor not used in scoring Series II
†—Interpretation of clinical status incorrect
‡—Interpretation of therapy status incorrect
§—Topectomy
¶—Lobotomy
CL24—Control erroneously entered as patient

QUANTITATED IDENTIFICATION OF PSYCHOSIS BY BLOOD SAMPLE DISCUSSION

Harry A. La Burt, M.D., Chairman

CHAIRMAN, HARRY A. LA BURT: I recognize Dr. Angrist.

DR. ALFRED ANGRIST: I would want to say, for the record, that I have really been most impressed by the equipment and the development of these instruments and particularly from the standpoint of the application of the instruments to the study of the *process* of clotting. Having for many years been toying with the problem of clotting in some of the cruder formats of the instrumentation that have been available to us, I can see in this particular setup infinite possibilities of application. But, therein is one of my concerns as far as its application here tonight.

Of all the biological systems that we have to deal with in the human body, the process of clotting is one of the most complex. I don't know how many variables enter into it, with everything controlled to begin with, and that means controlling many of the factors which were here admittedly not controlled.

You are dealing with a complex biological and biochemical system in which at least ten different known specific ingredients enter, with activators and inhibitors, and most of the factors are still probably unknown; but those that are known are very complex and variable indeed, and subtle.

It would seem then, that before a test of this type is applied in the abstract, because that is what you have done, for "quantitated identification" and *diagnosis* of such intangible states as psychoses and the like, much fundamental work is needed. From the standpoint of known physical and chemical changes, as far as biological science has yet established, we should first take this beautiful instrument, as it has been developed, and apply it to the action of clotting under the known variables that have already been expressed and the known aberrations of clotting in disease. Learn something about the clotting mechanism before applying it pragmatically to diagnosis. If you can do that, you can make a most important contribution, and then with that information in hand, you can apply it to the variations that occur in the mentally disturbed patient or whatever your specific nomenclature may be.

I am mindful of numerous tests that have been devised by the use of blood in diagnosis. There was a man who achieved considerable fame, and then infamy, by the adaptation of a blood test, a method of clotting blood on a slide, and applying it to the diagnosis of cancer. He had many supporters. Recently, too, only within a few years—you are all aware of the famous Huggins test, applied to the diagnosis of cancer. It is nothing more than the application of the clotting or coagulation process. We don't hear of it any more. It has gone the way of all flesh.

I would also mention this fact, and I hope I am not taking too long. We have had in our hand, in the biology laboratory, a test that has stood the test of time under varying conditions—the ordinary Wasserman complement fixation and the precipitation tests,—and yet no laboratory man would state that they represent tests in the sense of diagnosing a group of patients who had syphilis as separated from a group who did not, because we know of the variation, no matter how selective you make your antigen or how specific. There is an overlap that will always occur in the biological processes because of subtle influences, as far as blood serum is concerned.

Let me just mention one or two that I can point out as important here. The nutrition of the patient was controlled, but that doesn't control your fibrinogen factor, thrombin levels, AC globulin, your thrombin inhibitors, the trypsin content of the blood, your antitrypsin and the various other inhibitory factors;—all of these will play a part in the curve you have here. What is more promising is that, by prolonging the period of the process of clotting, you obtain a continuing curve: therein lies probably the most important application to the understanding of the clotting mechanism. Unscramble some of these variables first by such curves, and then apply it all to the problem of dichotomizing analysis and diagnosis. That would seem the proper approach as I understand biological science, rather than the broad overall empirical application to a field that is empirical enough as it is. No mathematician or statistician can solve an equation with too many unknowns and comparable insufficient known factual data with unknown relationships.

I would say, by way of concluding, I do not mean to belittle this effort. I think it is a remarkable procedure to have even evaluated this group of cases by this means. I think that the instrumentation is most remarkable,—I have never been more amazed by a demonstration, and I have been in the laboratory field for the last twenty-five years. To repeat, I have never been more impressed. I have also been most impressed by the painstaking mathematical analysis of these curves. The possibilities are infinite, but they should be applied first to the more basic fundamental processes. Until we do that, we are selling our fundamental scientists down the river. We are putting them up a blind alley, instead of down the road that is going to branch out into most fertile fields.

I do wish to commend those who have brought to light the application of an instrument of this kind to the problem of blood clotting, than which there is no more complex mechanism that I know of, and for which we need every bit of help we can get in the understanding of its complexities.

CHAIRMAN, LA BURT: Dr. Lang, who is Assistant Commissioner of the Department of Mental Hygiene in Albany, will you say a few words?

DR. H. B. LANG: Well, I have had the good fortune to have some advance information; so I have had a chance to collect some of my thoughts. The possibilities and the implications inherent in this test as it stands at the moment are rather frightening. I am convinced that the investigators have shown a statistical validity that can be accepted as of the present. For that reason there should be every support for further investigation.

We must, however, always keep a cautious side look available to ourselves. I put the biometrician on the spot by demanding proof, check, and recheck; then I had our own statistician go after him, and then our own statistician went after me. When we got all through with the day's argument, we were satisfied as to the soundness of the scoring and the results of the scoring. We cannot foresee what it means, nor what its full implication may be for psychiatry. It does represent for the moment a tool by which we can separate out at least two groups, possibly a third.

I myself am rather frightened at its predictability in treatment. That is something we have never had. We have had to rely on subjective opinion. Subjective evaluation in estimating healing, healing rate, level of recovery, or improvement sometimes are vitiated by our own personal involvement in the interpersonal relations. We cannot form an accurate scientific opinion. We can form a valid clinical observation, though. This gives us a precise tool. It is something that has been required in psychiatry and will be of inestimable value.

Dr. La Burt, it has been a pleasure to be here.

CHAIRMAN, LA BURT: Thank you, Dr. Lang. We are deeply appreciative of your message tonight. It is heartening indeed.

If there are no further questions or discussion, I shall ask Dr. Arthur Sackler to please close.

DR. ARTHUR M. SACKLER: Dr. Lang, in stating that he was frightened by the implications, expressed our own reaction when this material came through. We have, as you might have noted, very carefully refrained throughout the whole course of the papers from going too far beyond the scope of psychiatry. We realize full well the implications which Dr. Angrist hinted at, and many of which we are eager to get at. However, work of that sort requires a considerable amount of equipment and material. Nonetheless, it is planned and will go forward.

We must point out that the present studies were preliminary and limited and revealed an accurate differential between blood of psychotic and nonpsychotic on the basis of physical and mathematical scoring.

We can always report that the scores are affected by medications, e.g., histamine and sex steroids. It is our hope that actual analysis of this material will enable us to indicate which factors are being altered by the different endocrine substances. Such identification could then enable us in turn to recognize relative deficiencies and develop guides for therapy. As most of you know, we have long been convinced of the relationship between endocrine disturbance and psychosis and pointed out two years ago that such a dysequilibration is, in our opinion, related to the pathogenic mechanism. At that time, on the basis of our findings, we predicted that cortisone and ACTH would produce psychosis.

I want to express the appreciation of our entire group to the State, to Drs. Bigelow, Lang and La Burt. This work would not have been possible without their support, and whatever merit there is in the work, I think a good measure of the credit is due to them.

CHAIRMAN, LA BURT: I see one of our well-known Internists, Dr. Macfarlane. He must be able to contribute something to the discussion from the internal medical point of view.

DR. J. R. MACFARLANE: I haven't much to add. I did wonder, in taking blood from a group of undernourished or poorly nourished people, how that would be when compared to the controls?

DR. SACKLER: When we first got our results, we began to look for possible sources of error. One of the first possibilities considered was the nutritional status. It was then that we included a group of the out-patients with good nutritional status. Our accuracy of identification was higher than the in-patient group. Thus, in a way, we attempted to adjust for possible differences in hospitalized patients' nutritional status as compared to controls.

DR. MACFARLANE: I would like to add another thing. I have never been so impressed at a presentation of a paper, at the excellent coordination of mathematics, medicine, and psychiatry. I think it was a wonderful demonstration. I also feel, the fact that this instrument can and should be applied in the basic sciences does not change the real significance of the findings presented here tonight.

These men have not interpreted their findings in the light of the still not understood variations of the clotting mechanism. They have shown that, with a very high degree of accuracy, these graphs fall into identifiable patterns sufficiently characteristic that without foreknowledge of the case under study, they can be used for the purpose of a diagnostic adjunct and possibly providing a key to information of complex and far-reaching importance. I think this is the thing we must consider here tonight in the critical evaluation of this paper.

CHAIRMAN, LA BURT: May I express my thanks to each member of this group for being with us. I trust that your time has been well spent.

Oral Nonspecific Therapy

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Selye has noted that conditions in which symptomatic improvement is noted following the administration of ACTH are also benefited by nonspecific therapy. The inference is obvious. Since ACTH is known to suppress the body's reaction against antigen and allergen, those conditions benefited must be due to infection or allergy or both.

Chronic infection and allergy have a broad base in common since it is difficult to differentiate the systemic symptoms and often even local signs and symptoms of one from the other. Blood sludging is probably one of the most important common denominators. The capillary pattern of the individual, as well as whether the offending agent is reagenic or nonreaginic or antigenic undoubtedly will affect local lesions.

In considering one phase of the problem—infection—the upper respiratory tract lends itself readily to study because of the almost universal incidence of chronic infection and the frequency of acute infection in this site.

The experienced observer will note a rather sharp transition between these two types of infection subjectively. During the acute infection, the "alarm" reaction induced deliberately is mild and does not appear to advance the infection toward termination. At the junction between acute and chronic, however, the experienced observer will recognize that from this point on good reactions may be expected and rapid resolution of the residual infection will occur. The above suppression cannot be said to be true of the "second"[1] type of nonspecific reaction, however, since this may be noted by the experienced observer to occur spontaneously and intermittently during an acute infection of the upper respiratory tract. (In prolonged experience with three agents inducing the "second" type of reaction: sulfur, vitamin B_{12} and lecithin, I found that the reaction is most intense upon first contact with the agent, lasting three to five days.) As the reaction becomes less intense, it develops a recidivating character, reaching its peak in the afternoon or evening. This recidivating character is more typical of the natural reaction. The second type of reaction cannot be produced at will, however, and, if the new agent is taken daily, may not occur for a week or more after the first dose. For this reason, a given agent used at a given time (but not the reaction) may be easily discredited.

Probably a shift in enzyme relationships is important in the transition between acute and chronic. Since it is known that neither leukocytosis nor antibody rise, nor fever are necessary for an effective nonspecific reaction, the enzyme changes, as emphasized by Petersen[2] must be seriously considered as the exhumation of nonspecific therapy proceeds.

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In my own studies of the effect of certain agents in chronic infection, sulfur was found to be an unusual agent in that it was capable of inducing both types of nonspecific reaction. Five mg. of colloidal sulfur taken intramuscularly by the author induced the "second" type of reaction. A transient "alarm" reaction was induced by 100 mg. of sulfur taken orally, followed by the "second" type of reaction lasting about 48 hours. An oral dose of 200 mg. of sulfur induced an "alarm" reaction lasting about 24 hours followed by the "second" type of reaction lasting another 12 hours. On myself 200 mg. of sulfur induced the "peak" reaction, i.e. raising the dose did not increase the reaction. However, many individuals did not react to this dose of sulfur or when a total dose of 400 mg. was given. When these individuals were given 2 Gm. of sulfur, however, reactions occurred. The reason for this is obvious when it is considered that from 10-40 per cent of sulfur taken orally is absorbed. Tolerance developed to this agent, however, so that it was necessary to raise the dose weekly. The larger dose of sulfur was given in a malt syrup fortified with biotin, Vitamin B_{12}, etc., and alpha-tocopherol was given in capsules to be taken along with this preparation.

Libenson and Wittenborn[3] state that sulfur and gold both attach themselves to –SH groups but that sulfur, unlike gold, does not destroy these groups. Certainly sulfur is known to be a much safer agent than gold and probably for this reason. Since sulfur was reported to produce a rise in glutathione in the blood, Wheeldon[4] followed the glutathione value in a number of patients receiving small doses of colloidal sulfur, but noted no appreciable change in the blood titer. It may be significant that a fall in the glutathione value did not occur as there is evidence suggesting that a fall occurs during the "alarm" reaction[5]. The reaction produced on the author by taking 1 Gm. of glutathione orally on several occasions simulated the BAL reaction in mild form. The interchangeability of these two agents in protecting an animal against alloxan diabetes has been recognized[6].

Berkley[7] used lecithin many years ago in the treatment of Graves' disease and neurasthenia. The exophthalmos and other symptoms of Graves' disease responded well to lecithin. The symptoms did not return upon withdrawal of the drug if taken over a period of some months. Lecithin has also been found to be of value in psoriasis[8]. An oral dose of 100 mg. of lecithin taken by the author induced the B_{12} (second) type of reaction.

Quinine was used by Forchheimer[9] in the treatment of Graves' disease with marked benefit in the exophthalmos and other symptoms. Five grains of quinine taken orally by the author induced the "alarm" reaction. Using neither of these agents, I obtained the same benefit from foreign protein or other types of nonspecific therapy in a small number of cases of exophthalmos, with or without hyperthyroidism or a history of hyperthyroidism. Exophthalmos usually recurred in some patients following reinfection of the upper respiratory tract.

Reid[10] states that salicylates produce a definite type of reaction, which, if understood, would cast some light on the basis of rheumatic fever. (Thirty grains of acetylsalicylic acid taken orally by the author produced the B_{12} type of reaction.) Salicylates have been shown to inhibit hyalouronidase[11] and one wonders whether this effect is specific or is characteristic of any agent inducing the B_{12} type of nonspecific reaction. In any case, the recent studies of Haas[12] on the body's enzyme defense against bacterial invasion are pertinent. Haas showed that hyalouronidase is an invasion factor secreted by bacteria.

This is neutralized by an antienzyme in human serum. The "antinvasin" titre was high in healthy individuals.

The nucleins and yeast were noted by Petersen[2] to be capable of inducing the nonspecific reaction. (Forty mg. taken intramuscularly by the author induced the B_{12} type of reaction.) Recently adenylic acid (MY-B-DEN)* has been reported to be of value in a number of diseases, including arthritis. The physiological effects have been studied by Drury[13].

Jacobson's solution was discussed by Petersen[2] under the heading of cinnamic acid salts and esters. (One cc. of Jacobson's solution taken intramuscularly by the author induced the "second" type of reaction.) Kopetzky[14] has used this preparation in the treatment of patients with tinnitus, deafness, and vertigo, particularly on those who gave a history of chronic infection of the upper respiratory tract or showed evidence of infection when seen. Markowitz[15] used the same preparation in chronic pelvic inflammation with definite benefit.

Agents inducing the second type of reaction have been found to be of value in certain virus diseases.[1] On the other hand, the benefits of quinine on *herpes zoster* are well known. Similarly Petersen noted reports of benefit derived from the use of diphtheria toxin-antitoxin in mumps. In using abortive therapy for any acute infection of the upper respiratory tract, I have always used the combined treatment since the "alarm" reaction itself may be expected to abort some bacterial infections, if given early[2]. In four cases of mumps in which I used the combined treatment, the result was dramatic. Coriell[16] reported evidence of the spontaneous occurrence of the "alarm" reaction in poliomyelitis. The administration of ACTH in some cases did not appear to affect the disease. However, it seems likely that, since poliomyelitis is a virus disease more benefit would be expected from the "second" type of reaction.

Yellow bone marrow was given by Griffiths[17] to a number of patients with "colds", with good results. The result is not surprising in view of the fact that 36 minims of yellow bone marrow extract (Armour) taken by the author induced the B_{12} type of reaction.

Israel and others[18] reported the use of inositol (an agent inducing the "alarm" reaction)[1] along with other vitamins in treating patients with *angina pectoris* and other conditions in whom hypercholesterolemia was found. Marked symptomatic improvement occurred as well as a fall in the blood cholesterol. However, the cholesterol level began to rise after several months of treatment while treatment was still in progress. Conn and others[19] have shown that a sharp fall in blood cholesterol occurs during adrenocortical activity (using adrenocorticotropic hormone as the stimulus), and believed that the blood cholesterol esters were probably converted into adrenocortical hormones. With the "alarm" reaction produced by inositol, a drop in blood cholesterol may therefore be expected to occur. As tolerance develops to the agent, however, a rise in blood cholesterol may be expected.

There can be little doubt, in any case, that the benefit derived from the use of many agents in cardiovascular disease is nonspecific, i.e., is due to the favorable effect on the patient's chronic infection. Page[20] has reported the use of a vaccine given intravenously to patients with malignant hypertension. The treatment was given empirically, i.e. no

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attention was paid to the upper respiratory tract or other foci. Page concluded that the malignant phase of hypertension may be reversed by this type of treatment.

Currie and Will[21] reported the use of ascorbic acid intravenously, along with desoxycorticosterone intramuscularly in the treatment of arthritis. To the two patients who improved after treatment, he gave intravenous injections of saline as a control. Since they improved following the control injections, the conclusion was drawn that the treatment was of no benefit. Four Gm. of ascorbic acid taken orally as a single dose, by the author produced a mild "alarm" reaction (cf. Cranswick)[22]. Since, as Petersen noted many years ago, saline injections will induce the nonspecific reaction, the fallacy of the above conclusion is obvious.

In its present state, the oral nonspecific therapy which I have been using is as follows:

Rx	Biotin	0.1 mg.	
	Vit. B_{12}	6.25 mg.	Rx
	Folic Acid	0.409 mg.	Alpha-tocopherol - 100 mg.
	PABA	200 mg.	
	Inositol	250 mg.	Sig - 3 twice weekly
	Lecithin	100 mg.	
	Trypsin	100 mg.	
	D T D. Caps # 20		
	Sig. 2 twice weekly		

The capsules are given together as a single dose. The dose for a child before the onset of puberty is one-half the adult dose. The dose of Alpha-tocopherol is raised to 400 mg. after the second week of treatment in adults. By way of explanation of the above prescriptions: biotin, inositol, trypsin and alpha-tocopherol produce the "alarm" reaction. Biotin prevents exhaustion of the reaction, alpha-tocopherol is a "primer" (presumably forming an ester with inositol after ingestion)[23]. The addition of trypsin[2] to the formula greatly retards the development of tolerance to the "alarm" reaction agents. Lecithin and Vitamin B_{12} produce the "second" type of reaction. Tolerance to lecithin apparently does not occur. Folic acid is given because of its intimate relation to Vitamin B_{12}. PABA is given to prevent fatigue following repeated reactions to infection[1]. Patients were seen at the end of two weeks, thereafter at three or four week intervals.

In a series of 118 consecutive patients seen in a practice limited to internal medicine, only one showed no evidence of chronic infection of the upper respiratory tract and gave a negative history of the infection. No focal reaction occurred after two weeks of treatment. Seventeen patients were not seen after the first visit and were discarded from the study. Eight patients were not seen after two weeks of treatment and were also discarded. None of the patients had been previously treated by me. Seven patients were children under puberty. Of these a presumptive cure was obtained in five and treatment was incomplete in two. Of the 85 adults treated five weeks or more, 43 or 50.5 per cent obtained a presumptive cure. Nine of these reached this point in five weeks. In one patient presumptive cure of infection was reached after 27 weeks, the longest period treated in which cure was

obtained. In general, the occurrence of colds during treatment delayed cure, but, aside from this, patients in whom treatment was prolonged were less likely to reach presumptive cure (and, if cured, it has been my experience, are more likely to have a recurrence). In one patient, the presence of silicosis made the end point in the upper respiratory tract uncertain. Fourteen patients are still under treatment after 16 weeks or more. Twenty-six patients were lost after from five to 16 weeks of treatment. One patient died after 14 weeks of treatment following a syncopal attack. He had been much improved, but died of overexertion. He had had syncopal attacks occasionally for one year. The diagnosis was rheumatic heart disease, aortic stenosis, mitral regurgitation. Only three patients could be considered hyporeactors. The remainder (not cured) obtained satisfactory reactions and improved but fell short of cure during the time treated. In these, when possible, treatment will be continued indefinitely in order to maintain the improvement. The oldest patient was 78, the youngest 19 months. Two children had colds during treatment. Of the adults 31 or 36.4 per cent had acute infections of the upper respiratory tract during treatment. Patients were treated during the months of January to May during which time the "flu" epidemic occurred. Twenty-six patients had major or minor allergic manifestations (30.5 per cent). Needless to say, special attention was given to these with the idea of removing allergens from the environment. Although nonspecific therapy is good desensitization treatment, it has little effect on the manifestations of food allergy. As wide a variety of "entities" was found in the patients treated in this study as in the study previously reported.[24] Probably 50.5 per cent represents the minimum cure rate since some who did not return for re-examination were known to have had a good result. The "biologic cure" rate[24] was not determined since patients were advised to take the capsules at the onset of any acute infection of the upper respiratory tract after discharge, and to continue treatment twice weekly if the infection was not aborted.

COMMENT

The results of oral treatment of chronic infection of the upper respiratory tract compare favorably with those obtained using subcutaneous foreign protein therapy[24], so much so that I have found no reason to revert to the old type of treatment. In addition, oral nonspecific therapy is pre-eminently more feasible and lends itself to universal and prolonged, or frequent intermittent use. Undoubtedly, it can be further improved, but in its present state it offers an answer to innumerable patients for whom, otherwise, there is no satisfactory answer.

SUMMARY

1. The similarity between many of the effects of allergy and chronic infection is emphasized.

2. The action of certain agents in nonspecific therapy is discussed.

3. The results of oral nonspecific therapy of chronic infection of the upper respiratory tract using a combination of vitamins, trypsin, and lecithin are given.

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GENERAL PRACTICE CLINICS

VOL. 8 NO. 11 NOVEMBER 1951

CONFERENCE ON WORLD POPULATION PROBLEMS AND BIRTH CONTROL*

POPULATION AS A WORLD PROBLEM

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There is danger that in speaking of "population as a World Problem" people will assume there is but one population problem of prime importance. This is especially likely when this problem is defined as the ability of the world to provide the necessities and decencies of life for its present population and the probable increase. When the problem is defined in these general terms, it seems to me rather meaningless. There are many population problems which affect a large part of the people of the world and in this sense population are world problems. It is much more helpful, however, to think in more concrete terms, such as the population problem of Japan, of China, of India, etc. Thus, the famines or food shortages of any large country, while they create world problems, are not immediately due to the same causes as those in another country. Hence, the cure for famines in India may not be the same as that for food shortages in Japan.

When any large country has difficulty in caring for its population this fact is of concern to all the world, but there is at present no way in which the world as a whole can contribute substantially to the solution of the population problem in a particular

*Presented here are abstracts of the Conference on World Population Problems and Birth Control which was held by The New York Academy of Sciences on October 19 and 20, 1951. The original papers will be published in a monograph by The New York Academy of Sciences, Annals Series.

country. The growth of population in X is regarded by X and by most of the rest of the world as X's problem and X will accept no advice except as it sees fit. Actually the help that X is prepared to accept quite frequently does more harm than good, and or is not what Y is able or willing to give. Frequently Y cannot offer X fundamental help because it interferes with X's ideas regarding national sovereignty, or X fears it may be an entering wedge to foreign exploitation.

Again, Y may take actions to improve its own economy which may aggravate X's economic troubles in caring for its population. Y may impose import quotas, exchange controls, or enter into bilateral or group trade conventions which adversely affect its trade with X and even cause great hardship in X. X can do little or nothing to change this situation. Thus, while in many respects we live in *one world*, we are actually unable to act as though we were an integral part of one world. We live in a world in which every country can harm every other by actions taken to improve its own economic conditions, but in which the improvement of conditions in other countries requires carefully planned and coordinated action between nations. This is extremely difficult to secure, as we have seen in the League of Nations and the United Nations.

There is also a widespread feeling that the population problem of the world is solely an economic problem which can be solved by increasing production—the Colombo plan, Point 4 program, etc. This leads to ignoring the basic fact that every little economic improvement thus achieved may make future improvement more difficult for some countries because of the accelerated growth of population following these small improvements. This accelerated growth is likely to last for several decades, from the time when the death rate begins to fall in X until the time when its birth rate begins to fall faster than its death rate.

Increased production which worked pretty well in the West for about 150 years because of the relative abundance of new land cannot work so well in the more crowded parts of the world which are just beginning to feel the effects of the decline of the death rate. They have little new land to be brought into cultivation, and emigration on a scale large enough to offer even a breathing spell is quite unthinkable. We are driven to the conclusion, therefore, that each country has population problems peculiar to it and that there is no general world population problem, although a slower rate of population growth in most countries would give more time to seek an enduring solution. It does not take much study to convince most students of world conditions that the populations of the X's in this world will grow too rapidly to be cared for during the next several decades if we keep on doing things which will reduce the death rate while we do nothing to reduce the birth rate. The death rate cannot be reduced to the low level our science will permit and held at this level if we do not begin to take measures to reduce the birth rate to much the same degree. The present high birth rate countries do not have the margin of safety in new lands to exploit which the Western countries had in 1800, when they also had high birth rates; and it is open to serious question whether the application of science to production can make up for this lack of new land. Certainly it cannot do so for long. Hence, the reduction of the birth rate is a world problem.

but at the present time X will allow no country or group of countries to take any action which might further such control over population growth. It seems highly probable that we will get ahead much faster with the difficulties arising from the relatively rapid growth of population if we think of the population problems of X in the concrete and do not try to lump all the problems of all countries together as a simple world problem having a common solution.

BIOLOGICAL AND CULTURAL FACTORS AFFECTING HUMAN FERTILITY

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The ability to defer death presents modern man with a number of urgent problems in the field of politics, sociology and economics, of medicine, and of ethics. The vastly greater efficiency in human reproduction, now easily possible, can virtually eliminate some kinds of human suffering. It can—and is—magnifying other kinds of human suffering.

It may contribute to our understanding of these problems to consider briefly how the processes of evolution work as they have been revealed by researches in paleontology, ecology, and genetics. Darwin's brilliant writings of nearly a century ago put the problem of human fate on this earth in a wholly new light. Baldly stated, the variability of living organisms—achieved through gene mutation and the gene recombinations, which are continually being assembled by sexual reproduction, expose a vast array of variant organisms to elimination by the selective forces of the environment. These selective forces act as a biological veto reminiscent of the behavior of the Russian delegate to the United Nations Security Council. The environment says an emphatic and final "NO" to most of the vast array of variant combinations. Those fortunate catenations of genes which do survive to reproduce reveal again among their progeny some new mutations and many new combinations. Again the environment "chooses" the few and discards the many.

Among the organisms which have been exposed to this relentless sorting process, one can trace up the phylogenetic tree of life a steadily increasing efficiency in reproduction. That the species might survive, simpler organisms form many millions of ova each season. The female oyster, a creature by no means at the bottom of the scale of adaptation, spawns each year up to eighty million eggs that the species may survive. Reptiles and birds, which in varied degrees fend more effectively for their offspring, show a lower fecundity. At the top of the ladder of complexity stand the mammals which protect their young until development is far advanced. At the very apex stands man who protects his young after it has left the uterus of the mother by an elaborate social organization.

Even with the very high death rates which have characterized most human populations in the past, the efficiency of reproduction was great enough so that the problem of population pressure is by no means unique in this twentieth century. Among very primitive tribes anthropologists report a vast array of rituals and taboos whose purpose has been to space human births more widely. Norman Himes in his "History of Contraception" traces the development of ideas concerning fertility control from ancient beginnings in Babylon, China, and Egypt. Many of these depended on pure magic. They were hardly more effective than some of the quasi-ritualistic attempts to control fertility by taking one's temperature and making notes on a calendar.

Many of our ancestors took this question of population control so seriously that, if the incantations failed, direct action was often sanctioned. Infanticide was considered a lesser evil than mass starvation.

Today each babe brought to birth in the United States has an average prospect of better than sixty years of life. This marks a veritable new emergent in the evolution process. This new dispensation is at once one of hope and promise, but it has a darker side, if a balance of births and deaths is not achieved.

It is urgently necessary, therefore, that we who are privileged to live in this first century of the new vital age recognize the nature of the emergency which confronts us and somehow achieve an effective balancing of births and deaths.

Because of the very high death rates of the past ages, cultures have imbedded in them a well-nigh compulsive obsession with fertility. The accent on fertility rites found in many religions illustrates this. Much of the popular discussion of the population dilemma now facing all people accents this ancient conviction that an abundant fertility *per se* is a good and necessary thing. Even in tragically overpeopled regions, an increase in numbers still is called "favorable" by lay writers and demographers alike. This same obsession appears in the optimistic chorus swelled by economists (Schlichter of Harvard; Moulton of Brookings), chemists (Conant of Harvard and the Finish Nobel Laureate for 1951), physicists (Compton), astronomers (Kirtley Mather), that this already well-burdened planet of ours can easily provide for two or three or four times as many people as are today scraping a precarious existence from its surface. The actual, gruesome fact that the frantic scrimping of hungry multitudes merely to exist are destroying the productivity of large areas is egregiously ignored by these happy prophets of the millenium. As a consequence of this fixation, anyone who comes up with a cheery assurance about miracles of chemistry or the release of new energy by physics is sure of a wide and uncritical audience. To question the ethics of such pronouncements in the face of the grim reality is looked upon by some as well-nigh treasonable.

Without doubt, the extension to all of the world of the most advanced scientific know-how available in our best scientific experiment stations would make possible a very great increase in food production. Without any question, if this vast increase in food production could, by a miracle of education and a vast extension of technologic know-how, be extended all over the planet, there might be enough food for all on the day after this miracle occurred. If, at the same time, the question of the

effect this change would have on reproductive efficiency were ignored, it is certain that world population increase would be as rapid as it has been in some of the pilot plant explosion areas which our mixed thinking has already created. Any rational approach to this problem would recognize Puerto Rico, and more recently, Japan, as warnings of disaster just around the corner. If the population of the earth increased as fast as the population of Puerto Rico is now increasing, or for that matter, the population of Japan or many parts of Latin America, the earth would have by the year 1975 not 2.5 billion human beings living on it, but 5 billion.

I do not say that these huge increases, which are theoretically possible, could ever actually happen. Any such population runaway would soon be stopped by mass famine. The dangerous thing which the optimists will not face is that such is the reproductive efficiency of the human race today that increases of this kind are theoretically possible. In the light of that possibility is it really intelligent and decent and humane to befog this most crucial issue of our time with double-talk which implies that the food supply of the world can be kept in step with any likely increase of people? This tragic failure in social timing will surely, in the light of history, be considered one of the critical failures of this age.

In order to maintain a reasonable balance in numbers of human beings on this planet of ours, birth rates must be lowered and one of the great areas of invention which challenges the ingenuity of humankind today is the need to find effective means in many varied social contexts for this lowering of birth rates.

Then beyond that lies the challenge of selective births whereby the increase in defect and the loss of adaptability, which abrogation of selection entails, will be prevented.

As I see it, that is the great problem of this vital age, and it is in such a context that the more specialized discussions in the later sessions of this conference must be evaluated.

THE EFFECT OF PUBLIC HEALTH DEVELOPMENTS UPON POPULATION GROWTH

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All biological organisms must adapt themselves to their environment if they are to continue to survive either as individuals or as a species. Man is no exception to this general principle of adaptation. But unlike other biological organisms, man, to an increasing degree, can modify and control his environment.

This partial control over his environment is relatively recent in the history of mankind. Throughout most of the centuries of its existence, the human race undoubtedly has had a birth rate, which if unrestrained, would have resulted in standing room only throughout the world many centuries ago. But, until very

recently, this excessive fertility has been controlled, just as for all other forms of life, by an almost equally high mortality. The size of the population in any area has been held in check by war, pestilence, and privation.

That this must have been so can be illustrated by a simple arithmetic computation. At present the total population of the world is increasing at the rate of about one per cent per year. If their descendents had always increased at this same rate, the present population of the world could have developed from the offspring of a single couple whose first child was born about the time of Julius Caesar.

It is easy to forget how recently man has gained control of pestilence and privation, and even now this control is restricted to a minority of the world's population. About 1750 the death rate in London was in the neighborhood of 40 to 50 per thousand. In many large cities the annual number of deaths exceeded the number of births, so that the population was maintained only by immigration from rural areas.

Famines also were common until recently. It is estimated that there were about 200 famines in the British Isles between 10 and 1846 A.D. From one fourth to one third of the population of Europe probably died in a few months during the "Black Death" epidemic of 1348. Even as recently as 1846, nearly ten per cent of the population of Ireland perished in a severe famine. Others escaped death only by emigration.

The Industrial and Agricultural Revolution which began around 1750 in England radically affected the role of pestilence and privation in controlling population growth. Around 1650 the population of Europe was about 100,000,000, or 13 per cent of the world's population. By 1933 the descendents of this population numbered at least 720,000,000, an increase of sevenfold, and comprised some 35 per cent of the population of the world. How was this unprecedented upsurge in population possible?

Three factors were of prime importance in increasing man's control of his environment: (a) the development of commerce which made possible the transportation of food over long distances, (b) the opening up of new continents which provided new sources of food and an outlet for surplus population, and (c) technological changes which made possible a more effective utilization of natural resources.

The removal of the positive restraints upon population growth resulted in a rapid increase in population. However, before this increase again brought about a condition of biological equilibrium, man developed a new check upon population growth, namely birth control. This made possible the maintenance of a stationary or slowly increasing population by means of a low birth rate and a low death rate, whereas, in the past, control of the size of a population was achieved primarily by a high death.

This demographic revolution, however, has been characteristic only of a small proportion of the world's population. Most of the population of the world still has been controlled by the age-old forces of war, pestilence, and privation. Today roughly 60 per cent of the world's population has been relatively untouched by the demographic revolution.

All of the advances of the past 200 years in health, medicine, and the production and distribution of food are available for application in removing the natural checks

upon population growth, that is, disease and famine. The demographic revolution in Western Europe took nearly two centuries to run its course. During this interval, population increased nearly seven times before the birth rates and death rates once again approached equilibrium.

It seems almost impossible for the demographic revolution of the remainder of the world's population to run the same course as that for the population of Western Europe. The upsurge of the European population started from a base of about 100,000,000 and increased seven times. The nations now ready for the demographic revolution have a population of more than 1,000,000,000. Moreover, the control of mortality now is possible within a much shorter period of time than formerly. The primary demographic question facing us today is, how can the advances of public health and medicine be made available to all peoples of the world and at the same time keep birth and death rates in close enough balance so that the benefits made possible by the control of mortality are not nullified by a rapid increase in population.

CONTROL OF CONCEPTION IN CROSS-CULTURAL PERSPECTIVE

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The material for this paper has been selected from the available information on 190 different societies. These people live in markedly different environments, have widely varied customs and traditions. The purpose of this paper will be to show what similarities exist cross-culturally with respect to the control of conception and to point out some of the ways in which people differ in this regard.

In cross-cultural perspective, the control of conception has two distinct aspects. First, those practices which relate to increasing the probability of conception, and second, those practices which relate to the prevention of conception.

Attempts to induce conception appear to be characteristic of all the societies in our sample. Nearly every group provides traditional measures for counteracting "barrenness" in the woman. Related to these measures is the fact that most people regard the "barren" woman with either pity or contempt. Several societies provide standard recipes for "impotence" in the man. The practices designed to counteract "barrenness" and "impotence" vary in probable effectiveness from ones which are likely to have no usefulness, to ones which may actually be quite effective.

Similarly, practices relating to reducing the probability of conception appears to be generally present in all the societies in our sample. Such practices range from purely magical rites to techniques of effective contraception. Of particular interest in this connection is the fact that many peoples forbid intercourse to a mother during the lactation period, a matter of two to three years, or even longer. The justifications for this vary widely from one society to another, but the effect is a regular spacing of children which would otherwise not occur.

This study has indicated that some controls over conception, many of them ineffective, and others unknowingly effective, exist in all human populations. Any attempts to introduce scientific methods of controlling conception will compete with the traditional means of control already present.

Therefore, the first step in changing the practices relating to conception in any society will be to analyze the controls as they exist in custom.

PRESENT-DAY INTERNATIONAL TRENDS IN FAMILY PLANNING

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The population of the world is increasing at a rate faster than ever before, and, at the same time, the fertility of the soil is rapidly declining. Already nearly two-thirds of the world population—about two out of every three of the men and women and children on the face of the earth—are without the basic necessities of life. Millions of people are living at a mere subsistence level and are constantly faced with actual starvation.

The solution to this great human problem lies in two directions. Global steps can be taken to improve and increase food production, and international measures can be developed to stabilize human fertility. Only in this way can a better balance between the number of people and the resources of the world be brought about.

England. Planned Parenthood clinics have been in existence in England for more than a quarter of a century, and the Family Planning Association has for many years functioned as an active and effective organization. The English attitude on family planning was expressed in the official report of the Royal Commission on Population published in 1949. "We take the view," the Report reads on one point, "that it is in the long-run interests of the family that voluntary parenthood should become universal and that women should have the maximum freedom in the ordering of their lives."

Scandinavian Countries. Equally liberal is the attitude toward family planning in Sweden and the other Scandinavian countries. The Swedish Association of Sex Education has for many years been conducting education in family planning and has established a number of contraceptive centers in Sweden. The Swedish Population Commission, which published its reports in 1935-1938, stressed the importance of voluntary parenthood as a means toward a democratic family and population policy. Clinics also exist in Norway and in Denmark.

Holland. Holland was among the first countries in the world to establish contraceptive services. In the 1930's, well-equipped clinics under medical direction were opened in Amsterdam, Rotterdam, The Hague, and other cities. Following the German invasion, all the clinics were closed, but since the war a new association has been organized and, despite considerable religious opposition, family planning services are rapidly expanding.

Germany and Austria. During the Weimar Republic, after the First World War, Germany had a progressive and active planned parenthood movement, and many clinical services under the direction of the Health Insurance Association, the so-called Krankenkasse. With the coming of the Nazi regime, all the centers were closed, medical education in the field of fertility control was stopped, and the publication of medical literature on the subject ceased. In some parts of Germany there is at present a reawakening of social and medical interest in the problem of contraception, although the Nazi restrictive laws still prevail in many sections. It is quite likely that during the next decade, as a result of public pressure for information and material, a new planned parenthood movement will emerge in Germany.

France, Italy, Belgium. In Western European countries where the Catholic religion is the predominant faith of the people, the sale of contraceptive materials and the dissemination of planned parenthood information are prohibited by law. The rhythm method of family planning, however, is probably being increasingly practiced in many Catholic countries.

The Near East. At the present time there is no organized family planning work in any of the Arabian countries. A few individual physicians from these countries have obtained training in contraceptive techniques and are giving advice in their own practices, but such services reach only a very small portion of the population in these areas. Since the Moslem religion is not opposed to the prevention of conception, the opposition to contraception in Arabian countries is based primarily on social and cultural factors.

Israel. In Israel, too, there is no organized movement for family planning, but a few contraceptive services have been established in hospitals and in the social insurance medical departments. The public health authorities are at present giving some consideration to the question.

The Far East: Japan. A birth control organization was established in Japan some twenty years ago, but after the onset of the Sino-Japanese War, the government looked upon it with disfavor, and the clinics were later discontinued.

In 1949 the Japanese government established the Population Problem Council, with leading sociologists, economists, and educators as members. In its final report the Council stressed the dangers of overpopulation in Japan and recommended that "the national demand to check the population growth should find its support in the idea of voluntary family planning." At present a new and intensified planned parenthood movement is arising in Japan.

India. India is probably the most overpopulated country in the world, yet birth control measures are hardly known there. However, an Indian Family Planning Association was recently organized, and the government has fully recognized the vital importance of family planning for India. The Minister of Health of India has recently requested the World Health Organization to establish a pilot study on the use of the rhythm method of contraception in India.

China. What applies to India applies with equal force to China. There, too, populations are enormous, food supplies are meager, and the need for some form of

fertility control is urgent. A few centers exist in the larger cities, but little is known of present developments in this area.

Behind the Iron Curtain. Information is meager about family planning in the Soviet Union and in the countries that have hitched their wagon to the red star. As far as we know, no prohibitive laws against the dissemination of contraception have been enacted, but the entire social and cultural pressure is for a larger population and against the use of methods for controlling fertility.

The United States. The rapid acceptance and diffusion of family planning practices in the United States has been one of the significant social phenomena of our history. Thirty years ago there was not a single birth control center in the United States, hardly a medical paper was published on the subject, and there was no instruction in contraception in any of the medical colleges. Today family planning centers have been established throughout the country, contraception has become a recognized part of medical training, and research in the field of human fertility and its control is now being carried on in a number of our leading universities and laboratories.

Interest in family planning is today developing rapidly all over the world. From reports that have come to the International Committee on Planned Parenthood there are at present some forty areas in which family planning services are either available or where organizations for education in the field have been established. Among these areas are Australia, Austria, Barbados, Bermuda, Canada, Ceylon, Denmark, England, Egypt, Finland, Germany, Holland, Hong Kong, India, Italy, Jamaica, Japan, Malaya, New Zealand, Norway, Pakistan, Puerto Rico, Singapore, South Africa, South Pacific Island, Sweden, Switzerland, and the United States.

The worldwide need today is for practical, reliable, and inexpensive contraceptive methods. There can be little doubt that through the combined efforts of the laboratory and the clinic a contraceptive which will meet these requirements will be developed.

MEDICAL AND MEDICO-SOCIAL INDICATIONS FOR CONTRACEPTION

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For whom should a physician prescribe contraceptives? If the question were for whom should he prescribe insulin, or even penicillin, there would be a relative unanimity of opinion, because in such cases purely medical matters are involved. However, the field of conception control is medicine diluted by religion and social mores. A particular doctor's answer to the question, "Who should receive contraceptive advice?" is not only influenced by his religion and his social stratum, but his age, his medical-school training, the hospitals in which he practices and his medical

specialty. In the main, the younger and more recent graduates are the more liberal in their attitude.

In 1947 the author sent a questionnaire to fifteen thousand physicians scattered throughout the United States, one-third specialists in obstetrics and gynecology, two-thirds general practitioners. The purpose of the questionnaire was to establish a cross section of medical opinion in regard to conception control. Some 3400 physicians replied, of these only seventy-four stated that they did not approve of contraception for any medical condition, leaving a striking majority—97.8 per cent who believed that at least some health problem necessitated contraception.

In addition to the purely medical aspects of the survey, these 3400 physicians expressed approval or disapproval of conception control for other reasons. Eighty-six per cent approved of contraception for child spacing, 79 per cent for economic reasons, and 72 per cent as an aid in marital adjustment. The final question asked was, "Do you approve of contraceptive advice being given to any married woman who requests it?" In other words, does the physician believe that it is every woman's medical birthright to get the best scientific birth control knowledge available. To this very broad question, 68 per cent answered "yes," 29 per cent disapproved of such wide dissemination of contraceptive information, 1 per cent of the physicians had no opinion, and 2 per cent did not reply to the particular question. If this questionnaire mirrored the opinions of a representative cross-section of American physicians, which we believe it did, one may say that in their heart of hearts, seven out of ten doctors feel that any married woman desiring birth control information is entitled to it.

To return to the more purely medical aspects of the survey of physician attitudes, we sought to determine the commoner health problems for which doctors most approve of conception control. The question asked was—"Do you approve of conception control for the following conditions (assuming conditions are more than minimal)?" Twelve common health problems were placed in alphabetical order, and after each ailment there was a blank space to be checked under "yes," and a space to be checked under "no"; "yes" meaning approval of the ailment as an indication for birth control, "no" meaning disapproval. The answers are very interesting. No one indication polled 90 per cent approval, although almost 98 per cent of the answering doctors approved of conception control for at least some medical reason. The most popular medical indication proved to be cardiac disease, because 89 per cent of the doctors approved of giving birth control advice to cardiac patients. Eighty-seven per cent approved of pulmonary disease as a medical indication for conception control. The ten remaining medical conditions were listed by the doctors in the following order—renal disease, nervous and mental disease, great multiparity, hypertension, diabetes, exophthalmic goitre, prevention of inherited disease or malformations, recent pelvic operation, general debility and anemia, and finally venereal disease. This least popular health reason received approval by 66 per cent of the physicians.

The above data summarize then the general medical attitude toward conception control, primarily the attitude of the physician to strict medical indications. With

the above as introduction, I would like to express my own forthright opinion, in regard to medical and medical-social indications for conception control.

First, what are my medical opinions? The goal of every pregnancy is a healthy normal baby, born to a mother whose life is neither temporarily jeopardized nor permanently injured by its advent. If this formula be broadly applied, it will determine what pathological conditions make pregnancy ill advised. Whenever pregnancy is contraindicated, either contraception or sterilization is indicated.

If the pathological condition may be temporary, irrespective of the patient's age, contraception is indicated; sterilization ruled out. On the other hand if the condition interdicting pregnancy is permanent with no likelihood of improvement, sterilization is the wiser choice. This is particularly true if the woman is young with many fertile years ahead. An example might be in order. If the woman is a carrier of hemophilia, or has given birth to a series of abnormal children, sterilization is wise and proper. On the other hand, if her portion is to bear erythroblastotic children, a disease but recently unraveled, which is constantly being worked upon, contraception is preferred to sterilization. I say this, because in the next 12 months someone may discover a method of preventing erythroblastosis; for it is not a germ plasm defect, but simply an immunization reaction on the part of the body to a foreign substance which the host herself does not posses,—Rh factor.

What is my attitude toward medico-social problems involving conception control?

I believe that young people should be put in the position to marry while still young without the harrassment of impending pregnancy, pregnancy before they are economically or emotionally prepared for it. For intellectually mature women, premarital contraceptive advice by a physician is extremely wise. Sexual adjustment at the beginning of marriage is much better mental hygiene, than maladjustment to be followed by remedial measures.

Children are tragic cement to glue together a marriage separating at the seams. If there is any doubt about the stability of a marriage, postponement of children is very important until the disharmonies are securely adjusted.

It does not require a physician to point out the economic necessities for conception control. I dare say that most underprivileged couples who produce an annual model do so not from choice. Furthermore, the jurist, doctor, and social worker are similarly aware of the tie-up between poverty, huge families, and juvenile delinquency.

The problem of contraceptive advice for the unmarried is a very complex one. I am unwilling to accept the ostrich-like moralistic viewpoint that such a problem does not exist. It did not require the Kinsey report to prove that premarital intercourse is a general practice. I readily admit that I cannot give the proper answer to the question, "Should the youth of our country be scientifically advised and instructed in birth control?" Furthermore, I do not believe you can. The proper answer must depend on more Kinsey-like studies. Knowledge must replace taboo and prejudice.

Finally, there is the world picture, the inter-relation of population density and population growth with the standard of living and the geographical area of a political unit, problems which have already been discussed by experts on this program.

This then is one physician's attitude to the medical and medico-social indications for contraception.

BIOCHEMICAL STUDIES OF THE FEMALE GENITAL TRACT

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Cyclicity of reproductive capacity in the female is a fairly uniform feature among the mammals. In the normal woman, from menarche to menopause, as in most of the animals studied, the entire reproductive tract at quite regular intervals shows striking changes, seemingly designed to facilitate the union of the spermatozoa and the newly matured ovum, and to aid the growth and implantation of that ovum in the event of its fertilization. If pregnancy is not realized, the background for fertilization regresses and then is again prepared. These cyclic changes are under the control of the pituitary and the ovarian hormones and appear to depend not only on the absolute amounts of these hormones, but also on their ratio and sequence.

The cyclic changes in the female reproductive tract are expressed both structurally on the cellular level, as evidenced by the methods of histology, and functionally in terms of the dynamics of cellular metabolism. In comparison with the thorough histological examination of the female reproductive tract, the biochemical examination, especially in the human, is in its infant stage; and it is this less complete, often confusing aspect with which we are here concerned. Those tissues which provide the immediate environment of the spermatozoa, the ovum, and the fertilized egg will receive emphasis. Certain natural limitations on experimental work with human beings require that voids in their known biochemistry must, for the time being, be filled in with data from the far more abundant knowledge derived from lower animals, recognizing that conclusions from experiments on one species do not necessarily apply to others.

In contrast to the intra-uterine deposition of spermatozoa in some mammals, the deposition in the human female would seem to provide the sperm with an unfavorable environment. The normal vagina is acid in all phases of the cycle. This results from the breakdown of the abundant (and cyclically varying) glycogen in the vaginal walls. Acidity is detrimental to the metabolism of the spermatozoa and does not allow their motility to continue for any prolonged period of time. Fortunately, however, a number of spermatozoa quickly escape, at least during the ovulatory phase of the cycle, from the alkaline seminal plasma where it is deposited in the vagina into the propitious environment of the cervix.

The cervix, or more specifically its mucous secretion, undergoes pronounced cyclic changes which make it particularly receptive to spermatozoa during the four or five days of the ovulatory phase in women. The amount of secretion at this time is increased as much as tenfold, its water content rises, and its viscosity (as well

as the content of the complex polysaccharides probably associated with viscosity) drops sharply. While the scanty, thick mucus of the preovulatory and postovulatory phases appears to be almost impenetrable to spermatozoa, the abundant, runny mucus of the ovulatory phase has been shown to be easily penetrable by the sperm at a rate up to 3-5 mm. per minute and to support their motility for as long as 72 hours.

A number of the constituents of the secretion which would appear to be of importance to sperm life and function have been investigated to determine whether this cyclic penetrability of the cervical mucus is due to other chemical changes as well as to those involved simply in the physical state of the mucus. None of these constituents alone, however, has shown a cyclic variation favoring penetrability during the ovulatory phase above the other phases. Sodium chloride is present in a concentration which favors greatest longevity of the sperm. Furthermore, the secretion is, in the majority of cases, alkaline. Since human spermatozoa require certain carbohydrates for energy for their motility and undoubtedly can carry with them little supply from the seminal plasma on migration through the mucus, perhaps of great significance is the presence in the mucus of the utilizable carbohydrates, glucose, maltose, and glycogen and an enzyme, diastase, which breaks down glycogen to the more readily used glucose and maltose. While the amino acids and lipids in the mucus apparantly are not utilizable for human sperm motility, they are felt to contribute favorably to the total environment.

In contrast to the cervix, the vagina, because of its acidity, constitutes a hostile environment to sperm. As the spermatozoa progress from the cervix through the uterus to meet the ovum, they continue to find propitious surroundings. The lining of the uterus, like that of the cervix, is alkaline during the ovulatory phase. Also the deposition of glycogen in the epithelial lining of the uterus has been progressing under the influence of estrogen. The significance of the high concentration of alkaline phosphatase in the endometrium at this time is as yet undetermined. That it may have a role in the lipid metabolism of the endometrium or in the increased protein production of the ovulatory phase seem to be likely possibilities.

The high concentration of glucuronidase in the uterine epithelium (and also in the vagina) during the first two-thirds of the cycle has been interpreted as an involvement of this enzyme in transport or metabolism of the ovarian hormones and possibly also in the incorporation of glucuronic acid in certain intracellular substances, such as the mucins.

The newly matured ovum, at some as yet undetermined moment in the ovulatory phase, is expelled from the ovary and enters the fallopian tube, which provides for its passage to the uterus. In the human, both glycogen and lipids are present in the epithelial lining of the tubes. Since the site of fertilization is the outer part of the fallopian tubes in most mammals, the chemical constituents of the tubes may well be of significance for the spermatozoa also.

Some of the respects in which the ovary, both before ovulation and after the *corpus luteum* has been formed following ovulation, has been considered in relating its unique metabolism to its very specialized functions are: the lipid metabolism and its possible connection with synthesis of the ovarian hormones estrogen and

progesterone; glycoproteins and their relation to follicular growth; and the possible importance of mucinolytic enzymes during follicle growth and at the time of ovulation.

Following ovulation, the uterine epithelium continues to prepare a suitable medium for implantation and nourishment of a fertilized ovum. Glycogen is deposited in still greater amounts, probably due to the enzyme phosphorylase which is present in particularly high concentrations at this time. Another enzyme, a diastase similar to the one in the cervical mucus, also shows an increased concentration, and is thought to be concerned with the breakdown of the glycogen to simpler sugars which are more readily utilizable by the ovum. It is of practical significance that glycogen lack in the uterine epithelium in this phase of the cycle has been correlated with abortion and sterility. The lipid content of the endometrium also shows a further increase at this time.

The changing pattern of enzyme systems with changing properties of the tissue has been reflected in the endometrium in measurements of anaerobic glycolysis, which is highest during the ovulatory phase and falls somewhat in this postovulatory period. The aerobic glycolysis is always low, and the oxygen consumption of the tissue remains fairly constant throughout the cycle. The technique of tissue culture has provided the perhaps very significant information that endometrium of the proliferative phase requires a high oxygen tension for normal survival, while that of the secretory phase can survive equally well anaerobically or at high oxygen tensions.

Biochemical examination of the myometrium, which constitutes the bulk of the human uterus, indicates that the same phosphate energy system may be functional here for the uterine contractions observed during the menstrual cycle as in operation in the contraction of other musculature of the body. The effect of the inorganic ions potassium, calcium, sodium, and magnesium on contractility of the uterus is also of interest.

Even from the incomplete evidence at hand, it may well be concluded that one of the principal chemical functions of the female reproductive tract is the nutrition of the sperm and ovum, with final emphasis on a fertilized ovum which is to be carried through pregnancy, and that each section of the tract seems well prepared in the normal individual to carry out this function. Any attempt at the control of conception must recognize the physiological emphasis on success of conception. Examination of the biochemical facts does, however, present many interesting possibilities on likely sites and mechanisms of such control.

THE BIOCHEMISTRY OF THE HUMAN MALE GENITAL TRACT

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The biochemistry of the human male genital tract largely is that of the ejaculate, inasmuch as the latter represents the virtual sum total of precoital and coital se-

cretions of Cowper's gland epididymis, vas deferens, seminal vesicles, and prostate. We must consider that a part of the total ejaculate actually is pre-ejaculatory, since, in younger individuals at least, there is a considerable amount of secretion during precoital sexual excitement, which probably is derived in great part from Cowper's gland and the prostate. This precoital secretion contains few, if any, spermatozoa and, from a functional point of view, may be considered as "lubricatory", probably contributing nothing directly to the process of conception. Again, considering the biochemistry of the male genital tract from the point of view of function, the secretions to which we should devote major attention are those of the testis proper, the epididymis, the ampulla of the *ductus deferans*, the seminal vesicles and the prostate.

The Testes. The chief biochemical function of the testicle is to provide the androgenic hormone, the secretion of which is essential for the maintenance of the accessory glands which, in turn, provide the secretions of the ejaculate. The chemistry of the fluid, formed in the duct system of the testes and acting as the medium for transport of the spermatozoa from the germinal epithelium to the epididymis, is virtually an unknown quantity. In the human, the spermatozoa pass from the seminiferous tubules to the epididymis quite rapidly, inasmuch as relatively few spermatozoa are found free between the germinal epithelium and the epididymis, a transit which involves traversing the straight ducts, the cavernous rete testis, and the efferent ducts.

The secretion (or secretions) of the epididymis undoubtedly is of great importance in the physiology of the male reproduction since all the evidence to date points (1) to a relatively long stay of the spermatozoa within this convoluted duct and (2) to a maturation process in the spermatozoa (probably chemical in nature and not morphological) within this reservoir. Again, it is an exceedingly difficult experimental problem to obtain epididymal fluid for analysis, and much of our meager evidence regarding it has been derived from hydrocele fluid.

The chemical contribution of the *ductus deferens* proximal to the ampulla is unknown and must be considered in light of the time taken for the spermatozoa to traverse this portion of the duct. The kinetics of this passage also are unknown, though there is reason to believe that the spermatozoa pass rapidly from the epididymal portion of the *ductus deferens* to the ampulla. Only one factor seems certain in the combined secretion contributions of the epididymis and the *ductus deferens*: no substrates are found which would initiate motility in the spermatozoa.

Anatomically, the ampulla of the *ductus deferens* is in close proximity to the seminal vesicle, and morphologically, the resemblance is equally analagous. Just prior to ejaculation, most if not all of the spermatozoa which are to be delivered in any particular ejaculate, are massed in the ampulla. By the use of certain techniques, we have been able to draw restricted conclusions regarding the chemistry of the fluid bathing the spermatozoa in the ampulla.

The seminal vesicles contribute by far the greater part of the human ejaculate volume. The epithelium of these sacculated glands also must be highly specialized since certain chemical transformations take place within its cells which are not

common to any other body cell, except those of certain embryonic tissues. For example, it has been shown that blood glucose is transformed to fructose in this epithelium and secreted into the vesicular fluid to form a substrate after the initiation of motility. Other aspects of the chemistry of the fluid of the seminal vesicle will be discussed.

The chemical contributions of the prostate gland to the total ejaculate are, as we have suggested, probably pre-ejaculatory and ejaculatory. It is difficult to dissociate the two contributions since much of the pre-ejaculatory portion is present in the urethra and is washed out in the first wave of the ejaculate. For the purpose of this discussion, the chemistry of the prostate gland will be considered entirely as ejaculatory.

Since we are discussing the ejaculate functionally, that is, as providing the chemical medium for the transport of the spermatozoa from the male reproductive tract to the female under the best possible conditions, we must consider the mechanism of ejaculation as well as the chemistry of the fluid forming it. We must also keep in mind that deposition of the ejaculate in the vagina is an integral part of ejaculation and that the chemistry of the ejaculate is such that it can offset, for a time at least, certain harmful influences which the vaginal environment can bring to bear upon the spermatozoa. In many mammals, including the human, the process of ejaculation is accompanied by a clotting of the ejaculatory fluid. This process requires a rapid interaction of the secretions of two or more accessory glands after ejaculation has been initiated. This coagulation process must be reversed (this happens rather quickly in the human) and requires the presence in the ejaculate of enzymes which will perform this function. It is possible that coagulation of the ejaculate is part of the defensive mechanism against the harmful influence of the vagina.

A CRITICAL STUDY OF METHODS OF MEASURING SPERMICIDAL ACTION

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Since the publication by Kölliker of the first organized spermicidal investigations almost one hundred years ago, several systems have been used to determine the lethal effect of chemicals on sperm. More recently these tests, which are actually widely diverse in procedure, have been used to develop more efficient spermicides and to compare the quality of various commercial contraceptive products. An analysis was made of these tests with particular attention to important details, such as the nature of diluents, the amounts of test substance and semen used, mixing techniques, temperature, and controls. It became evident from this intensive survey that no one existing test measures all the properties of contraceptive preparations, and that the test adopted by the American Medical Association as a requirement for acceptance does not yield

enough information nor permit comparative ratings.

This fact, plus the considerable contradiction existing between criteria for spermicidal action in the several tests considered, led to the development of two new tests by members of the staff of the Ortho Research Foundation. The first of these, the "Saturation" test, was designed to determine how much semen can be handled by a unit volume of contraceptive. In practice, as little as 0.05 ml. of the preparation is titrated with successive additions of 0.1 ml. semen until, under the conditions of mixing and timing employed, some sperm are seen to remain alive within a given time. The value of the formulation is expressed in volumes of semen in which spermicidal action is complete compared with the volume of contraceptive used. By this test there has been observed as much as a nineteenfold difference between preparations which bear "approval" by the ordinary tests.

Other properties of "barrier" and spermicidal nature are tested by the new "Zone" method. This test, which is relatively simple to conduct, depends upon the distance the sperm can migrate into a spermicidal preparation from a central pool of semen. A dilution of the contraceptive is covered by a coverslip containing a small central aperture filled with semen. With the aid of a micrometer eyepiece, the radius of the zone marked by the limits of migration from this central portion containing live sperm is measured. Generally, this zone is well-defined; its extent varies with the dilution of the preparation. Thus, when several materials are tested at similar dilutions, a scale of comparative values may be set up; the "best" preparation would be the one which permitted least penetration of the contraceptive material by the sperm. Here again, there are wide differences between various products.

To demonstrate these differences, five commercial contraceptive preparations were tested by four methods: the "standard" Brown-Gamble method, the Sander-Cramer method, the Saturation, and the Zone test. By the first of these methods, all preparations were of equal value. When the Sander-Cramer test was applied, two of the materials had equal and high potency, while the other three assumed relatively lower ranks. By both the Saturation and Zone method, the substances arranged themselves in slightly different relative order values. However, it is important to note that a new synthetic base gel designed as a "barrier" type ranked first throughout all tests. Thus, it is possible to determine whether a "superior" preparation is superior in all properties.

A brief historical review is included for purposes of orientation, as well as a discussion of the role of the laboratory in contraceptive research. Mention is made of a new biological test for contraceptives, employing the rabbit as the test subject.

A METHOD OF CONTRACEPTION WITHOUT DIAPHRAGM

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This study was undertaken because of the desire to find a simpler, more efficient means of planning parenthood. In this enlightened era the need for family limita-

tion is so well established that it is not necessary to elaborate extensively on the reasons for this desire. The Whelpton and Kiser study shows that 90 per cent of the couples under investigation tried to control pregnancy. The role of contraception in preventive medicine is widely accepted. Toland says that "preventive medicine (is) the promotion of health and happiness of individuals, rather than—an avoidance of something noxious."

Many married couples engage in sexual union with the thought that their indulgence will not result in pregnancy. Regardless of religious belief, every parent wishes to control the number of offspring. Much difference of opinion regarding the mechanics of implementing this wish prevails. The marked improvement in maternal and infant mortality and morbidity statistics in the last twenty years is due to the widespread availability of contraceptive information as well as the improved methods of treating these patients. A large number of the bad risks is screened out by conscientious physicians who prescribe contraceptive advice to these risks.

In evaluating a method the following points are considered: (1) Effect on the tissues. Absence of irritation. (2) Ease of administration. Simplicity is paramount. Mechanical occlusive devices may be difficult to insert and not widely applicable. (3) Suitability of the method from an esthetic standpoint. It must be nonodorous and nonstaining. (4) Ease of dispersion. The agent should spread rapidly throughout the folds of the vagina and should be easily miscible with the semen to ensure complete spermicidal action. (5) Rapidity of spermicidal action. (6) Proven fertility of the group under study.

The studies of Baker, Ransom, and Tynen suggest that the ideal contraceptive also be inexpensive, unaffected by the ordinary range of climate, and easily portable.

The material chosen for the study, Preceptin Vaginal Gel, is a smooth, white, odorless preparation containing as spermicides Ricinoleic Acid and p-Diisobutylphenoxyethoxy-ethanol in a synthetic base, buffered at 4.5. It possesses the following desirable physical properties: it spreads readily, mixes rapidly with vaginal secretions and with seminal fluid, and its superior adhesiveness favors adequate covering of the external os, as shown in the photographic slide. The Gel is nonirritating, as proved by the normal vaginal biopsies taken after 6, 9, and 16 months of continued use (slides).

Esthetic acceptability and effectiveness in preventing conception were ascertained through a questionnaire and by study of the charts. A predominant number of the 704 women in this study were of proven fertility. During the two year study of this contraceptive Gel, conception was effectively controlled in 98.2 per cent of the 704 patients.

CLINICAL EXPERIENCE WITH A NEW GEL-ALONE METHOD OF CONTRACEPTION

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The use of the jelly-alone in place of the standard diaphragm-and-jelly method is not new. Stein, Garvin, Eastman, and others found the former method about as effective

as the latter. The problem has been to find a contraceptive jelly which has physical and chemical properties sufficiently superior to render it more highly reliable. The results of clinical experience with such a gel are here reported.

Patients were instructed in the use and application of the gel and were required to keep on calendar cards furnished them a record of their menstrual periods and dates of coitus.

A total of 634 patients were given the new contraceptive, Preceptin Vaginal Gel, during the survey period. Of this number, 467 patients had used the gel for 2 to 22 months, giving a total of 4046 woman-months exposure. Charts show the woman-months exposure of this group and pregnancies in those patients using the method two to six months or longer (Group "A"), using it less than six months (Group "B"), and in those who returned calendar cards (Group "C").

Based on the estimated noncontraceptive pregnancy rate of 80 (Cavanaugh), and expressed in terms of failures per woman-months of exposure, the pregnancy rate in this study was 4.1 for the entire group. There were 5 pregnancies in the series of women using the gel six months or more, an effectiveness of 97.9 per cent. From the calendar cards it was seen that coitus was practiced at all times of the cycle, including the fertile period.

RECENT TRENDS IN THE STUDY OF INFERTILITY

A. OVARIES AND FALLOPIAN TUBES—WITH SOME CLINICAL CONSIDERATIONS OF THE MALE

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The most important advances that have been made in the study of human infertility concern themselves with a better understanding of the physiology of the reproductive process and the ability to demonstrate anatomic defects in the organs of reproduction. The complete and detailed investigation of the sterile couple usually uncovers the cause of the infertility, but it provides, in addition, the major therapeutic tool. Therapy has lagged far behind diagnosis in this important gynecologic problem.

Rubin's signal contribution showing the ease with which the patency of the human reproductive tract can be demonstrated provided the impetus for modern sterility studies. The normalcy of the reproductive organs can be ascertained by pelvic examination and by their visualization by radiopaque substances. The uterus and Fallopian tubes should be visualized as a part of every sterility investigation. Absorbable and nonabsorbable contrast media are available, but the consensus of opinion is that more satisfactory studies can be carried out by the use of nonabsorbable substances. The hazards in the visualization of the reproductive organs are

so small when a careful technique is employed that they need not deter anyone from using this valuable diagnostic aid.

Gas insufflation of the uterus and tubes should be used in subsequent procedures. It provides much information concerning the normalcy of the tubes, their peristaltic activity, and their patency. Kymographic tracings afford concrete evidence of these properties. Gas inflation when properly controlled can be repeated at periodic intervals and undoubtedly have some therapeutic value in the relief of partial tubal blockade.

The Speck test for tubal patency was introduced in 1948. It utilizes the principle that, when the dye phenolsulphonphthalein is introduced into the uterine cavity, it passes through the Fallopian tubes, if they are patent, and into the peritoneal cavity. It is rapidly absorbed into the blood stream and appears in the urine within a half hour. The simplicity of this ingenious procedure makes it applicable in any environment, but its accuracy is only about 85 per cent so that it will not replace the Rubin test.

In the absence of tubal blockade, at least 25 per cent of women become pregnant within an interval of four months. In our experience, this figure is higher when a radiopaque medium is used. There has been no satisfactory explanation for this phenomenon. Thus, the study of the reproductive organs provides a useful therapeutic, as well as a diagnostic tool.

The relief of tubal blockade has become a major interest of many individuals in the field of human infertility. In the past the results, following surgical procedures, were very poor, for less than 5 or 10 per cent of women achieved pregnancy. Advances in surgical techniques have provided new ideas for this special field. It is now possible to maintain tubal patency more easily by the use of plastic and absorbable tubes placed in the lumen during the operation. When the closure is at the ostium, a small cone-like absorbable tube can be inserted to maintain patency. Resection and reimplantation of the tubes into the uterine cavity are facilitated by the use of a plastic tube of very narrow diameter. One end is fed into the uterine cavity from which it can be removed through the cervix at a later date. Although too few of these operations have been done to date, the results are very promising.

Ovarian function can be studied by a variety of methods, all of which are indirect in character. The regularity of the menstrual cycles is a fair index of ovarian activity. The endometrium mirrors the changes that take place in the ovary so that endometrial biopsies represent an important feature of sterility investigation. Biopsies may be taken serially at weekly or monthly intervals. They are obtained easily, but they must be sectioned, stained, and studied histologically.

Basal body temperature graphs are extremely useful in following follicle growth, follicle rupture, and *corpus luteum* formation. Enough data has not accumulated to explain the mechanism of the temperature changes and to demonstrate some of the pitfalls in the interpretation of the graphs. Clinically, the recording of body basal temperatures has become the most useful method of following ovarian function.

Ovarian failure represents a challenge to students in the field of endocrinology and human infertility. The various hormonal substances used in the treatment of

ovarian failure are ineffective. The gonadotropic preparations offer promise, but at the present time the commercial preparations will not induce ovulation and *corpus luteum* formation in women whose gonads are not functioning normally. Chorionic gonadotropin will prolong the life and function of the *corpus luteum* for this is its physiologic role, but it will not stimulate follicle growth or induce ovulation.

Some work has been done recently on ACTH in ovarian failure. Although in a few instances it was possible to induce some irregular menstrual periods, the action was not sustained. Our data implicates the adrenal in the normonal pattern necessary to support normal ovarian function, but its therapeutic role is not promising at the present time.

The syndrome of polycystic ovaries and ovarian failure has been treated by Stein and others by wedge-shaped resections of these large gonads. Several recent reports confirm the good results obtained in some patients. However, a great deal more evidence will have to be forthcoming to demonstrate the value of ovarian resection. It is not a physiologic approach to this problem, and the vast majority of women who have gonadal failure have normal ovaries.

Hypophyseal gonadotropins offer the greatest promise in the therapy of ovarian failure. The recent advances in the endocrinology of adrenal function should spur investigators to isolate a gonadotropic hormone from the anterior lobe of the pituitary which will do for the gonads what ACTH does for the adrenal. It is logical to expect that a potent gonadotropic hormone from the anterior lobe of the pituitary will induce a follicle growth, rupture, and *corpus luteum* formation in women with gonadal failure.

Thyroid extract remains the most useful glandular preparation in ovarian failure. Its action is probably by way of the pituitary gland, and it has a useful therapeutic role in mild and moderate ovarian failures.

B. CERVIX AND UTERUS—EMOTIONAL ASPECTS OF INFERTILITY

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What has been done in recent years to help the infertile couple will be presented by two speakers. The first will cover some aspects of this problem and then will discuss the cervical and uterine factors in infertility. Just what the actual fertility of a given couple is can not as yet be determined. In a fair percentage of cases studied, both partners are by our present analytical methods entirely normal. Animal breeders know that some males as well as females are more fertile than others and quickly eliminate infertile ones from their breeding pens. This aspect of our problem is discussed at some length.

The emotional, psychological, or even psychiatic causes of infertility have been interesting more workers in recent years. The alteration of physiological and anatomical functions in all organs of the body by emotional disturbance is well known.

These intangible factors certainly play a large role in infertility and should be more thoroughly investigated and understood.

The cervix, both from anatomical and physiological point of view, has been under intensive study. We have long recognized that severe cervical infections or extreme stenoses would cause infertility. Minor alterations in the physical characteristics and chemical constituents of the cervical mucous are now thought to prevent conception. Tortuosities of the canal and minor stenoses play a definite part in this problem. Even the bacteriology or normal cervical mucous must be studied because certain bacteria are spermicidal. Excess or inadequate production of mucous associated with infection, stenosis, or endocrine imbalance are discussed. What is the actual role of the cervical mucous in sperm migration and sperm survival?

Malpositions of the uterus, uterine tumors, and abnormal variations in the endometrium have been felt to be factors in causing infertility, but students of the problem have differed for some time as to the number of times these abnormalities are causes. Too much has probably been said and written about hypoplasia of the uterus, and too many women have been given psychic bruises by being told that "their womb is undeveloped" when really a small uterus in itself is rarely a cause of infertility. Gynecologists and obstetricians have somehow obtained the idea that everybody's uterus has to be so big. They allow for no variation between individuals, and completely forget the fact that a uterus felt by bimanual examination in a nulliparous woman who is awake and tense may be an entirely different size under anesthesia. Naturally, genital hypoplasia in the underdeveloped female who menstruates irregularly and poorly can prevent conception, but, if a woman menstruates regularly and adequately, the size of the uterus is probably not a factor in her infertility. I cannot say how many times an obstetrical patient has told me that, at the time of her premarital examination, she was told that her uterus was underdeveloped and that she would have a difficult time becoming pregnant. She was, therefore, careless about practicing contraception and became pregnant almost as soon as she was married.

Malpositions of the uterus, particularly retroversion and retroflexion, have long been controversial causes of infertility. If the retroposition takes the cervix out of the seminal pool, it can delay or even prevent conception. In the absence of other cause of infertility, the use of a pessary or even a suspension is justified as a last resort. Often the uterus becomes out of place because of the presence of unrecognized endometriosis. Treating the latter and suspending the uterus often effects a cure.

The role of endometriosis in infertility has been so well covered in a recent issue of the Ladies Home Journal, that nothing more need be said about it, except to point out to that Journal that the new disease they write about was first reported and subsequently completely described in the medical literature over 30 years ago. That the incidence of this condition seems to be increasing is quite true, and its role in infertility is well recognized. Many of the abnormalities of the endometrium, particularly those that are the result of distorted ovarian function, will be discussed by the second speaker. We should mention, however, chronic endometriosis, passive

congestion due to malpositions, and the recently reported incomplete sugar metabolism in the endometrium as possible causes of infertility.

Uterine tumors may mechanically prevent conception, they may distort the endometrium sufficiently to prevent implantation, and polypi of the endometrium may by their presence prevent either the meeting of the spermatozoa and egg or interfere with the implantation of the fertilized ovum. The presence of fibroid tumors alone, even in the absence of any of the above changes, may in themselves be a cause of infertility. More and more when all else has been found to be normal, these tumors are being removed with an appreciable salvage of infertile couples.

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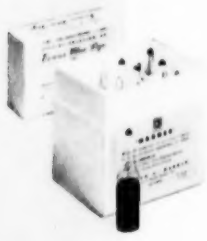

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